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MEMORANDUM

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Subject: Benchmark Dose Calculations on Thyroid Data from Studies Submitted for Evaluation of Perchlorate

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Attached are benchmark dose analyses of data from the 14-day "Caldwell", Subchronic, Developmental Neurotoxicity, Rabbit Developmental Toxicity, and Mouse Immunotoxicity studies. Benchmark analyses were run on corrected data sets provided by Kevin M. Crofton (section 5.2). Sources of these data are noted in the following text. Benchmark analysis was performed using the US EPA Benchmark Dose program (beta versions 0.96 and 1.1) and SAS software provided to AMG by Ralph L. Kodell.

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Introduction: Benchmark doses (BMDs) and the lower confidence intervals on the benchmark dose (BMDL) were calculated on data from five of six dose response studies submitted to the US Environmental Protection Agency (USEPA) as part of the perchlorate risk assessment effort. BMDs and BMDLs were calculated for the thyrotrophin (TSH), thyroid hormone (T₃ and T₄), morphometry and histopathology data, and, in one case, motor activity data from these studies using the USEPA Benchmark Dose software. BMDs were also calculated for the log transformed data in most cases. BMDs were also calculated using the Kodell-West algorithm (Kodell and West, 1993) to examine BMDs submitted to the USEPA.

BMDs for continuous data were calculated using a variety of benchmark responses (BMRs). The following tables include the BMD and BMDL generated with a BMR equal to a response 10% less than the control mean estimated by the function fit to the data. More specifically, 10% of the actual control response was subtracted from the estimate of the control value generated by the fit to the data. For the natural log (ln) transformed data, this means subtracting the constant 0.1053 from the control value, equivalent to multiplying the control value by 0.90. This is a less rigorous standard than the (control - 5% of control) standard that provided a close match to the NOAELs in the evaluation of continuous BMDs by Kavlock, et. al. (1995). Even given this standard, in many cases included in the tables below the BMDL is many times lower than the NOAEL or LOAEL. BMDLs at 20% and 30% less than control and control standard deviations are also provided as a yardstick for estimating how other criteria might affect the BMD and BMDL. Hormone data were fit with polynomial (linear or quadratic) or power functions (Table 1).

Adequacy of fit for continuous data was judged by the statistical goodness-of-fit (-2 * log(likelihood) ratio test) provided by the BMD program's output as well as a judgement of whether the fit was biologically plausible. The latter criterion meant that in most cases, non-monotonicities in the function fit to the data precluded a fit from consideration. The 2nd order (quadratic) fits in general suffered from minima or maxima between the data points from two highest doses in a given experiment. This consideration also precluded the use of polynomials of higher than 2nd order, since these higher order polynomials generally had local maxima or minima between data points (dose levels) and did not plausibly model the data. It should be noted that the interpretation of the test for constant variance included in the output of the version of the USEPA BMD program (version 0.96) used is not reliable.

BMDs and BMDLs were calculated for the incidence of thyroid histopathology as determined by standard histopathological observation, using a benchmark response of a 10% increase in incidence over control (i.e., BMD10, BMDL10). The histopathology data were re-coded to count any severity rating > 0 as an incident of histopathology. Data were fit with the whole gamut of functions available through the USEPA BenchMark Dose Software (Table 1). A chi-squared test was used to determine the goodness-of-fit of these functions.

BMDs and BMDLs were compared to NOAELs or LOAELs derived by analysis of variance (section 5.2). These comparisons can be seen in the tables included in Appendix A.

BMDs SUBMITTED TO US EPA

Two sets of BMDs were derived from the Caldwell study (14 day exposure to adult rats) and submitted to the USEPA (Dollarhide and Dourson, 1997). One set of BMDs was calculated for TSH and T4 levels for males and females separately using the THC (polynomial fit) module of the Crump program. THC restricts coefficients to be non-negative to prevent non-monotonicity. This resulted in linear fits to curvilinear data. For the T4 data, the fits badly underestimated control values (Appendix A1, Figure A1-1). For the TSH data, the fit to the female rat data overestimated control and the fit to the male data underestimated the majority of the data (Appendix A1, Figure A1-2). The goodness-of-fit statistic included in the output of the THC program indicated that these fits were not statistically significant (Dollarhide and Dourson, 1997). Recommendation: ignore this set of numbers.

BMDs were also derived using an alternative approach to calculating additional risk, the Kodell-West risk assessment algorithm. The Kodell-West (K-W) model (Kodell and West, 1993) generates a quadratic fit to the dose response data, uses a constant k times the standard deviation ($k\sigma$) to define an adverse effect level, then calculates additional risk based on the control distribution of the response variable. It uses maximum likelihood estimators to fit the regression function and confidence limits. The report including the K-W BMDs (Dollarhide and Dourson, 1997) did not include the coefficients of the quadratic fits or any measurement of goodness-of-fit.

To assess these fits, USEPA obtained SAS code from Ralph L. Kodell to run his model of calculating additional risk. Values of $k = 2$ or 3, corresponding to response levels occurring in 2.3% or 0.13% of the control population, respectively, were used for defining the adverse effect. The k value is independent of the additional risk specified. 1 % and 10 % additional risk were used.

The BMDs calculated by USEPA with Kodell's SAS program compare favorably to those previously reported (Appendix A1, Table A1-1) (data from Caldwell, et. al., 1995). Coefficients of the quadratic fits are reported in Appendix A1, Table A1-2. Small differences in BMDs between those calculated by USEPA and those previously reported may be due to a difference in the algorithm used to handle dose data. The extreme magnitude of the ratio of BMD/LOAEL for the $k=3$ adverse criterion for T3 and T4 suggests that this coefficient was too high, defining adverse levels of effect well beyond levels which were significantly different than control. The same was generally true of the 10% additional risk. USEPA also calculated BMDs on natural log transformed data (Appendix A1, Table A1-1), since the Kodell algorithm assumes constant variance and the transformed data is more likely to fit this assumption. BMDs calculated on the transformed data were virtually identical to those from the non-transformed data.

Plots of these functions and estimates of goodness-of-fit derived from the USEPA BMD program (which yields the same fit coefficients) show that the fits to the Caldwell male rat data were poor (Appendix A1, Figures A1-3, A1-4, A1-5, Table A1-2). The fits were non-monotonic over the tested dose range. As there was no evidence for a u-shaped dose response, these fits were not plausible. The global maxima or minima are listed for each endpoint in Appendix A1, Table 2. None of the fits to the endpoints listed in Table 2 reached statistical significance. These data were not amenable to fit by quadratic equations (see Appendix A1, pp. A1-9 to A1-14); this

obviates the use of the Kodell-West BMD.

BMDS GENERATED BY US EPA

Standard Histopathology Data

In general, all of the functions provided adequate fits to the data, and the BMDs and BMDLs for a particular study were within a factor of 2 or 3 of one another (Figures 1A and 1B).

The Quantal Linear, Weibull, and Gamma functions produced identical fits to the follicular hypertrophy data (incidence per litter) from the Developmental Neurotoxicity study (PND5 pups) (Argus, 1998a, York, 1998c), yielding BMDs of 0.234 mg/kg/day and BMDLs of 0.10 mg/kg/day, identical to the LOAEL determined by analysis of variance. The fits of the other functions yield slightly higher values (Appendix A7, Table A7-4, Figure A7-1).

Similarly, for the Caldwell study (Channel, 1998a), all of the functions produce BMDs within a factor of 4 of the LOAEL of 0.1 mg/kg/day for standard histopathological severity rating of follicular hypertrophy. Five of the six BMDLs calculated for this data are within a factor of 2.5 around the LOAEL (Table A7-1).

Benchmark dose calculations for the incidence of follicular hypertrophy/ hyperplasia in the Subchronic study (Springborn, 1998) yielded higher BMDs and BMDLs than for the Developmental Neurotoxicity and Caldwell studies, in keeping with the higher NOAELs obtained in this study. For the 14 day timepoint, all of the BMDs and BMDLs are within a factor of 5.5 of the NOAEL of 1.0 mg/kg/day. For the 90 day timepoint, the BMDs and BMDLs are within a factor of 2.5 of the NOAEL (Tables A7-2, A7-3).

Caldwell 14-Day Study (data from Caldwell, et. al., 1995)

Power functions successfully modeled the T3, T4, and TSH data from the combined male and female rats, i.e. statistically significant, monotonic functions (Appendix A2, Table A2-1). The BMDLs (BMR: 0.90*ctl) for TSH and T3 are 3 to 5 orders of magnitude lower than the NOAELs or LOAELs figured for the Caldwell data. Because different NOAELs were found for male and female TSH, BMDs were calculated separately for these endpoints. For female TSH, the BMD was approximately twice the NOAEL and the BMDL was one third of the NOAEL. Functions could not be fit to the male TSH data. For T4, the BMDL from the combined male and female data matches the LOAEL; the BMD is approximately three-fold greater than the LOAEL.. BMDLs calculated with BMRs of 0.80*CTL and 0.60*CTL are included for comparison (Appendix A2, Table A2-2).

The fits to the data assumed a constant variance. For the non-log-transformed data, this might not be a safe assumption for the T3 and TSH data. For T3, variance decreased with decrease in T3 level (and increasing dose); for TSH, variance increased with increasing TSH level (and increasing dose) (Data used for fits can be seen in Output of USEPA BMD program included in Appendix A2, pp. A2-4 to A2-11). Constant variance fits were likely appropriate for the natural log transformed data. Quadratic fits to any data were unsuccessful.

Subchronic Study (Data from Springborn, 1998)

14 Day Time Point (Appendix A3, Tables A3-1 and A3-2)

TSH data was fit by both polynomial and quadratic functions. The polynomial function has a maximum between the highest two doses. The power function provided a better fit to the data, based on the log(likelihood) goodness-of-fit statistic provided by the BMD software. The BMD point estimate was 4-fold higher than the NOAEL. The BMDL was more than 2 orders of magnitude lower than the NOAEL.

The T3 data was fit very well by a power function, but the lower confidence limit included 0, so no BMDL could be calculated. The BMD point estimate was 2.5 orders of magnitude lower than the LOAEL. The T3 data could not be fit by a quadratic function.

T4 data was fit by both power and polynomial (quadratic) functions. These two different fits yielded similar BMDs but considerably different BMDLs, with the quadratic BMDL 2.2 orders of magnitude higher than the power function BMDL. The BMDLs from the quadratic fits likely reflect some combination of a) a lower estimate of the control value (y-intercept) and b) a reduced slope of the quadratic function compared to the power function as it approaches dose 0. It should be noted that the quadratic fits have global minima at approximately the value of the high dose. The BMDs for T4 were of similar magnitude as the NOAEL.

90 Day Time Point (Appendix A3, Tables A3-3 and A3-4)

The TSH data were fit by a power function and yielded BMDs and BMDLs within an order of magnitude of the NOAEL.

T3 data could not be significantly fit by power or polynomial functions.

T4 data was fit by power functions, but the BMDL for T4 could not be calculated (BMDL for $\ln(T4) = 0.00$). The BMDs from the fits to T4 were 3 to 4 orders of magnitude below the LOAEL.

Rat Developmental Neurotoxicity Study (Appendix A4, Tables A4-1 and A4-2)

Data from PND5 pups were analyzed (Argus, 1998a, York, 1998c). TSH data were fit very well by both linear and power functions. These yielded BMDL/NOAEL ratios of 1.26 and 0.48, respectively.

T3 data could not be fit with any available function.

T4 could only be fit by a non-monotonic quadratic, with a shallow minimum between the two high doses. This fit produced BMDs and BMDLs nearly identical to the NOAEL.

Thyroid cell morphometry (lumen size) data were fit by a quadratic with a shallow minimum between the highest two doses (Table A4-1). This fit produced a BMD approximately equal to the NOAEL and a BMDL within 0.2 orders of magnitude of the NOAEL.

BMDLs were also calculated for the movement and time data from the motor activity test from post-natal day 14 pups. These data were fit by a linear function with fairly shallow slope, yielding BMDs for movement and time of 1.94 and 1.33 mg/kg/day and BMDLs of 1.04 and 0.66

mg/kg/day, respectively (Tables A4-3 and A4-4).

Rabbit Developmental Toxicity (Seg II) (Appendix A5, Tables A5-1 and A5-2)

Only T4 had a NOAEL; there were no effects on other thyroid endpoints. The BMD and BMDL bracketed the NOAEL by more than an order of magnitude on each side. (Data from Argus, 1998c; York, 1998e.)

Mouse Immunotoxicity (Appendix A6, Tables A6-1 and A6-2)

Again only T4 had a NOAEL. At 14 days of exposure, the dose response could be fit by linear, quadratic, and power functions (Table A6-1). The three function types yielded nearly identical fits (p-value varies because of the number of parameters fit for the different types of function). All three functions yielded a BMD of approximately 20 mg/kg/day. BMDLs were 2.89, 3.99, and 15.05 mg/kg/day for power, quadratic, and linear fits, respectively. The power function BMDL was nearly identical to the NOAEL. At 90 days of exposure, the T4 data was fit extremely well by a power function, but no BMDL could be calculated because the lower limit on the confidence interval included zero. The BMD was 1.4 orders of magnitude lower than the NOAEL. Linear and quadratic functions did not fit the data. (Data from Keil, et. al., 1998.)

DISCUSSION

BMDs and BMDLs were derived from fits to TSH, thyroid hormone, morphometry, and in one case, motor activity data submitted for the perchlorate risk assessment using a BMR equal to 0.90*Control response. BMD10 and BMDL10 were also derived for incidence of histopathology data from three studies.

BMD10 derived with a number of different functions for a dose-related increase in the incidence of thyroid histopathology showed good agreement regardless of the function used (Figure 2A). BMDL10 showed a slightly wider distribution (Figure 2B). The BMDs and BMDLs were in good accord with the LOAEls and NOAELs for standard histopathology.

There were no statistically significant effects in the motor activity data from PND14 pups from the Developmental Neurotoxicity study (Argus, 1998a). The BMDs and BMDLs calculated for the motor activity data from the rat Developmental Neurotoxicity study yielded values that could possibly serve as estimates of LOAEls and NOAELs for this data set. They are in accord with the mean values that may have emerged as significantly different from control had the data set not had its unusually high variability.

Many of the BMDLs that could be derived for the hormone data were lower than the NOAEL or LOAEL values arrived at by analysis of variance. Murrell, et. al. (1998) suggested that this occurs when sampling statistics, i.e., small group sample sizes and few dose groups, play a large role in inflating NOAELs while depressing BMDLs. This may be the case for some of the data sets examined here. They suggest that under such conditions, using the BMD point estimate rather than the lower confidence bound would be a more accurate result in terms of representing the dose-response behavior.

BMDs calculated with a benchmark response of 10% less than control on the TSH hormone dose-response data were spread over 2.5 orders of magnitude (Figures 3A, 4A), a similar range to that seen in the distribution of NOAELs calculated for TSH. The BMDLs were more widely distributed, over 5 orders of magnitude. These reflect the steepness of the confidence limits calculated at low doses.

T3 BMDs were spread over approximately 2 orders of magnitude, similar to the variability seen across studies in the LOAELs and NOAELs. The T3 BMDs were 1000-fold lower than the LOAELs/NOAELs, however. A BMDL could only be calculated for one of the datasets, and this was approximately 10,000 times lower than the LOAEL (Figures 3B, 4B).

The BMDs comprising the 25th to 75th percentiles for T4 (Figure 4A) covered the same 2.5 orders of magnitude covered by the range of T4 NOAELs and LOAELs. The BMDLs for this same percentile range were distributed a little more widely, but do include the dose range of T4 NOAELs and LOAELs.

An alternative reason for the low BMDs and BMDLs lies in the data itself. The thyroid hormone data had an extremely steep dose-response curve and were best fit by power functions with slopes < 1.00. This draws the biological plausibility of the power function fits into question. Crump (1995) suggested that fits with slopes that approach ∞ at dose 0 are biologically implausible and would likely reject such fits. However, Hasselblad, et. al. (1995) suggested that restricting the slopes of fits to the data prioritizes mathematical convenience over fitting the data. The thyroid hormone data in the submitted data sets do show exquisite sensitivity to very low doses of perchlorate. In some cases, only LOAELs can be calculated from the hormone data. This suggests that to fit models with non-supralinear slopes, lower doses needed to be used. The choice of doses in these studies, however, should not preclude modeling the data to the best of our ability.

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Crump, K. Calculation of benchmark doses from continuous data. *Risk Analysis* 15(1):79-89; 1995.

Dollarhide, J and Dourson, M. Reference dose for perchlorate. Abstract from "Conference on issues and applications in toxicology and risk assessment," April, 1997.

Hasselblad, V, Jarabek, AM, Svendsgaard, DJ, Davis, JM. Restricted versus unrestricted models: why is one the magic number? *The Toxicologist* 15(1): 178 (abstr. 952); 1995.

Kavlock, RJ, Allen, BS, Faustman, EM, Kimmel, CA. Dose-response assessments for developmental toxicity. *Fundamental and Applied Toxicology* 26: 211-222; 1995.

Kodell, RL and West, RW. Upper confidence limits on excess risk for quantitative responses. *Risk Analysis* 13(2): 177-182; 1993.

Murrell, JA, Portier, CJ, and Morris, RW. Characterizing dose-response I: critical assessment of the benchmark dose concept. *Risk Analysis*, 18(1):13-26.

Table 1. Functions Used in Benchmark Dose Modeling**Models for Continuous Data:**

Power function: $f(\text{dose}) = \text{control} + \text{slope} * \text{dose}^{\text{power}}$

Polynomial function

(includes linear and quadratic): $f(\text{dose}) = \beta_0 + \beta_1 * \text{dose} + \beta_2 * \text{dose}^2 + \dots$

Models for Dichotomous Data:

Gamma	$P(\text{response}) = \text{bckgrd} + (1-\text{bckgrd}) * \text{CumGamma}(\text{slope} * \text{dose}^{\text{power}})$
Logistic	$P(\text{response}) = 1/(1+e^{(-\text{intercept} - \text{slope} * \text{dose})})$
Probit	$P(\text{response}) = \text{CumNorm}(\text{intercept} + \text{slope} * \text{dose})$
Quantal Linear	$P(\text{response}) = \text{bckgrd} + (1 - \text{bckgrd}) * (1 - e^{(-\text{slope} * \text{dose})})$
Quantal Quadratic	$P(\text{response}) = \text{bckgrd} + (1 - \text{bckgrd}) * (1 - e^{(-\text{slope} * \text{dose}^2)})$
Weibull	$P(\text{response}) = \text{bckgrd} + (1 - \text{bckgrd}) * (1 - e^{(-\text{slope} * \text{dose}^{\text{power}})})$
Multistage	$P(\text{response}) = \text{bckgrd} + (1 - \text{bckgrd}) * (1 - e^{(-\beta_1 * \text{dose} + \beta_2 * \text{dose}^2 + \dots)})$

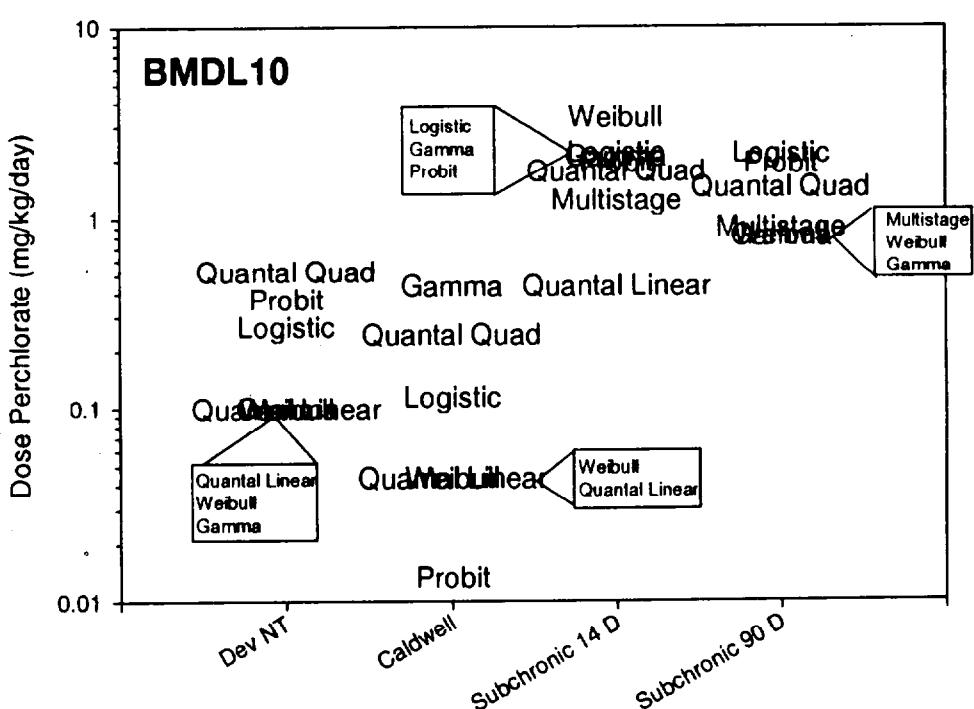
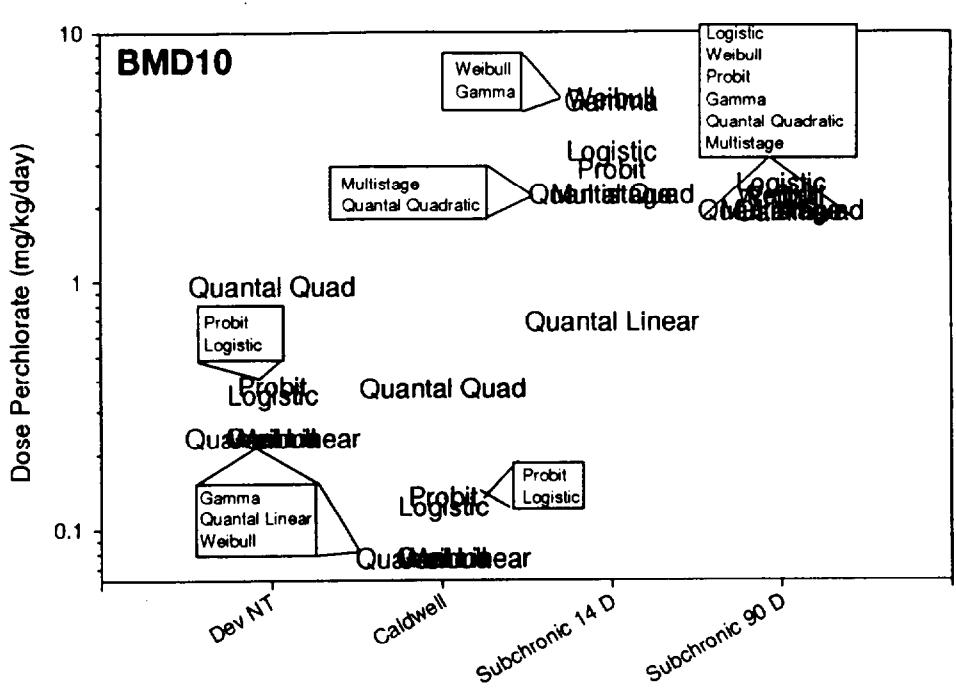


Figure 1. A (top) BMD10 and B (bottom) BMDL10 derived from the fits of a variety of analytic functions to the dose-response of incidence of thyroid pathology with perchlorate exposure.

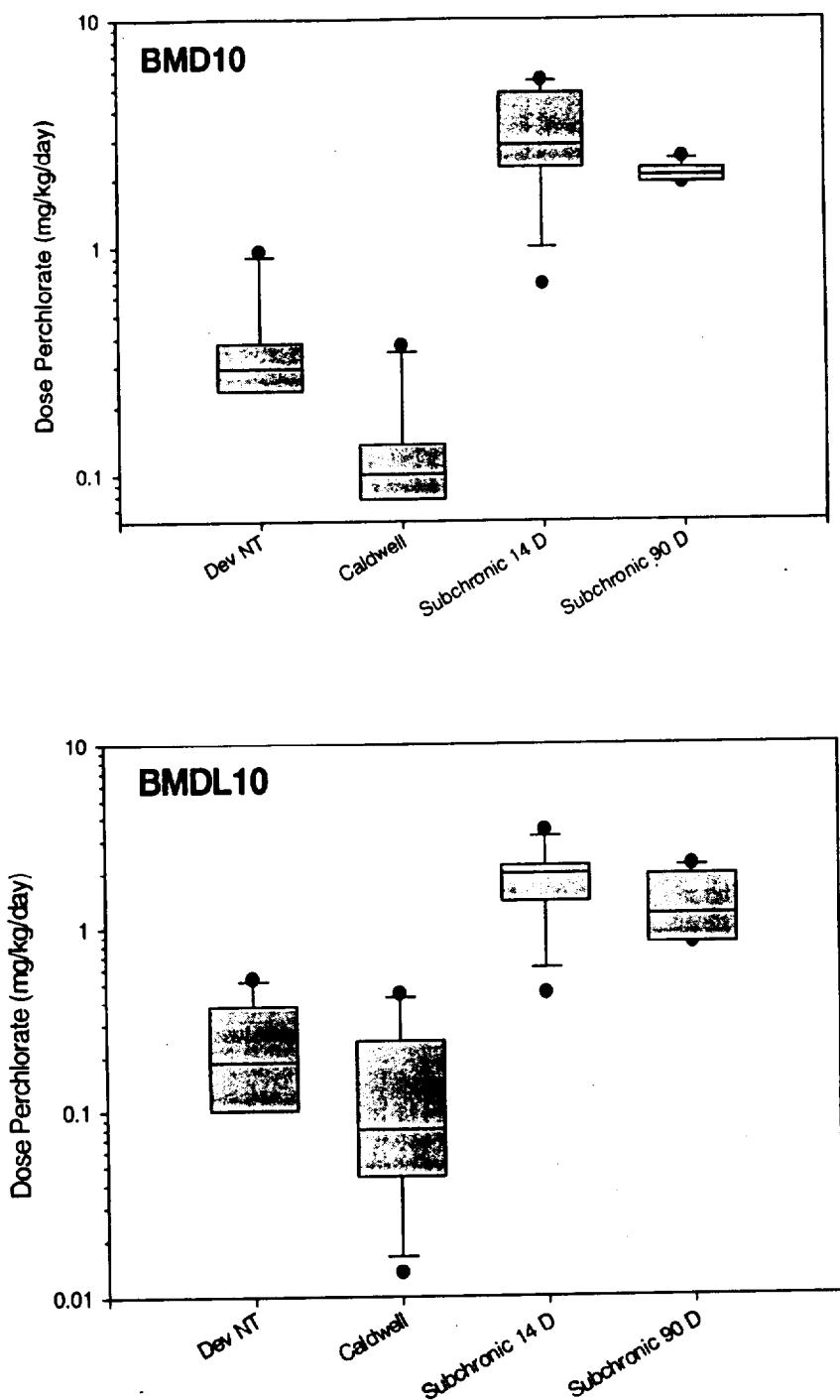


Figure 2. Box plots of A (top) BMD10 and B (bottom) BMDL10 derived from the fits of a variety of analytic functions to the dose-response of incidence of thyroid pathology with perchlorate exposure. Box outlines 25th and 75th percentiles with line at median, whiskers illustrate 10th and 90th percentiles, and points show outliers.

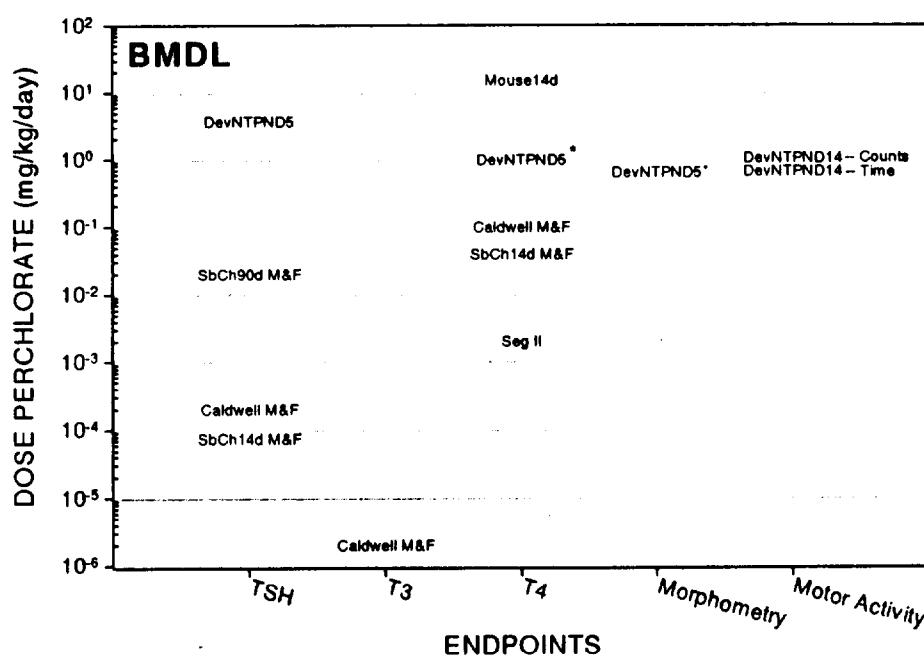
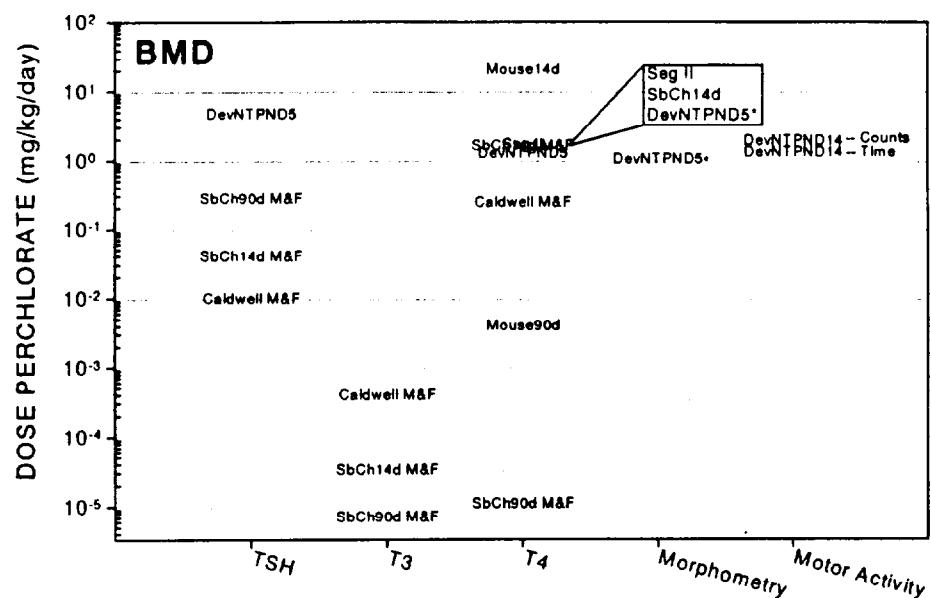


Figure 3. A) BMD (top) and B) BMDL (bottom) calculated for continuous data from a variety of endpoints for 5 studies submitted for perchlorate risk assessment. BMR was a 10% change from control value. Where multiple functions were fit for the same endpoint in the same study, the BMD(L) from the best-fitting function was used.

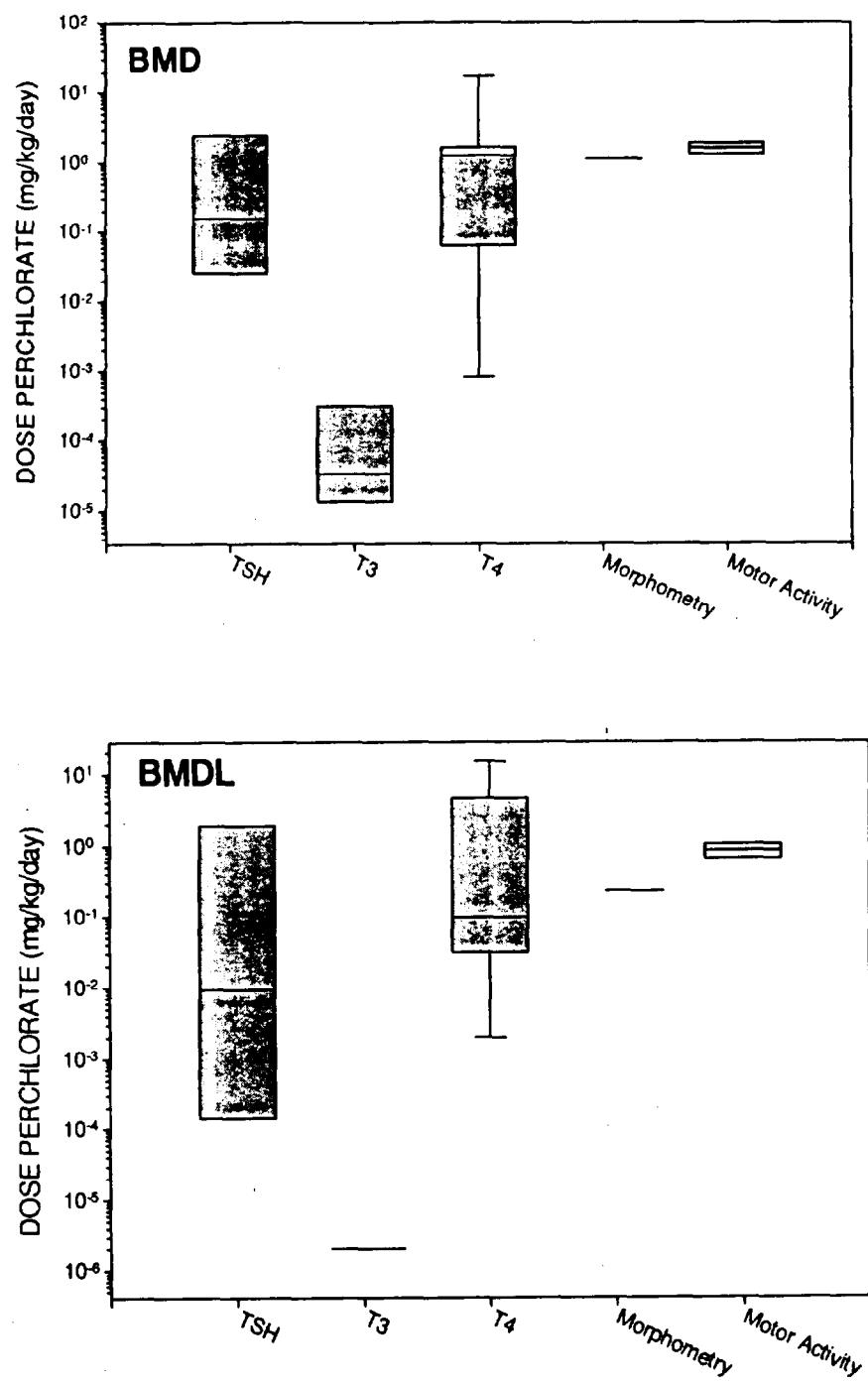


Figure 4. Box plots of A (top) BMD10 and B (bottom) BMDL10 illustrated in Figure 3. Box outlines 25th and 75th percentiles with line at median, whiskers illustrate 10th and 90th percentiles.

**APPENDIX A. BENCHMARK DOSE CALCULATIONS FROM DATA SUBMITTED
FOR PERCHLORATE RISK ASSESSMENT: TABLES, PLOTS, AND FIGURES.**

Appendix A1. Plots and Tables of Fits and BMDs calculated to examine BMDs from Caldwell 14-day study included in Dollarhide and Dourson, 1997.

Appendix A2. BMDs calculated for Caldwell 14-day rat study.

Appendix A3. BMDs calculated for Subchronic Study, 14 and 90 day time points

Appendix A4. BMDs from Developmental Neurotoxicity Study

Appendix A5. BMDs from Rabbit Developmental Toxicity (Seg II)

Appendix A6. BMDs from Mouse Immunotoxicity Study

Appendix A7. BMDs from Standard Histopathology, Caldwell, Subchronic, and Developmental Neurotoxicity studies.

Appendix A1. Plots and Tables of Fits and BMDs calculated to examine BMDs from Caldwell 14-day study included in Dollarhide and Dourson, 1997.

Table A1-1. Kodell-West BMDs calculated from Caldwell Study, male rat thyroid hormone and TSH data.....	A1-2
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Caldwell male rat quadratic fits.	A1-9
Polynomial Model male TSH	A1-9
Polynomial Model male ln(TSH)	A1-10
Polynomial Model T4 male	A1-11
Polynomial Model ln(T4), male	A1-12
Polynomial Model T3 male	A1-13
Polynomial Model male ln(T3)	A1-14

Table A1-1 – Benchmark Doses on Caldwell Male Rat Data Calculated Using the Kodell-West algorithm. USEPA refers to BMDs calculated using SAS software obtained by USEPA for Kodell-West calculations. D & D refers to BMDs included in Dollarhide and Dourson, 1997.

Responders	Dose associated with 1% Additional Risk (mg/kg/day)		Dose associated with 10% Additional Risk (mg/kg/day)		NOAEL or LOAEL / BMDF:N(L)OAEL 1%; 10%
TSH	USEPA	D & D, 1997	USEPA	D & D, 1997	1.11
k = 3	0.832	0.823	2.078	2.074	0.75; 1.87
k = 2	0.176	0.172	0.972	0.970	0.16; 0.88
In TSH					1.11
k = 3	0.845		2.115		0.76; 1.91
k = 2	0.181		0.987		0.16; 0.89
T3	USEPA	D & D, 1997	USEPA	D & D, 1997	0.11*†
k = 3	0.980	0.983	2.485	2.495	8.1; 22.59
k = 2	0.209	0.207	1.146	1.151	1.9; 10.42
InT3					0.11*†
k = 3	0.891		2.244		8.1; 20.4
k = 2	0.190		1.042		1.73; 9.47
T4	USEPA	D & D, 1997	USEPA	D & D, 1997	0.11*†
k = 3	0.797	0.658	1.969	1.639	7.25; 17.9
k = 2	0.172	0.136	0.927	0.774	1.56; 8.43
In (T4)					0.11*†
k = 3	1.002		2.490		9.11; 22.64
k = 2	0.215		1.169		1.95; 10.63

* LOAEL; otherwise, value indicates NOAEL † LOAEL from combined male and female

Table A1-2 – Coefficients of Kodell-West (Quadratic Polynomial) fits to Caldwell male rat data
 Coefficients generated using SAS software received from Ralph L. Kodell; identical coefficients
 were generated by US EPA BMD software.

Responders	B0	B1	B2	Dose mg/kg/day of Global Max/Min	p of fit*
TSH	17.182	2.895	-0.0914	max: 15.84	<0.00001
ln TSH	2.825	0.1269	-0.004202	max: 15.11	<0.00001
T3	112.871	-8.987	0.3169	min: 14.18	<0.00001
lnT3	4.7114	-0.09702	0.0034	min: 14.27	<0.00001
T4	4.7712	-0.1791	0.00445	min: 20.11	<0.00001
ln (T4)	1.563	-0.0414	0.0009	min: 23.00	0.00012

* p > 0.05 denotes significant fit. Goodness-of-fit derived using -2 log (likelihood ratio) test from USEPA BMD software (see pp. A1-9 to A1-14).

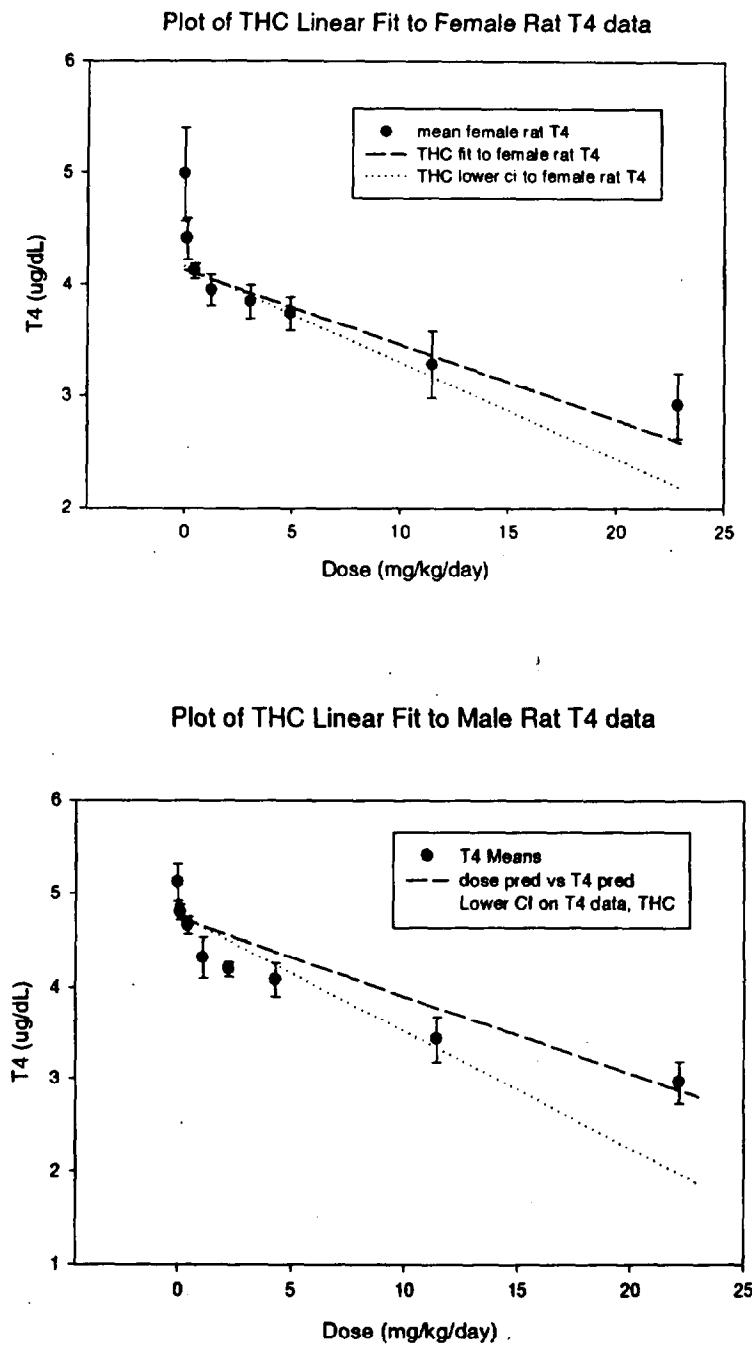


Figure A1-1. THC linear fits to T4 data from Caldwell study. Fits are statistically not significant.

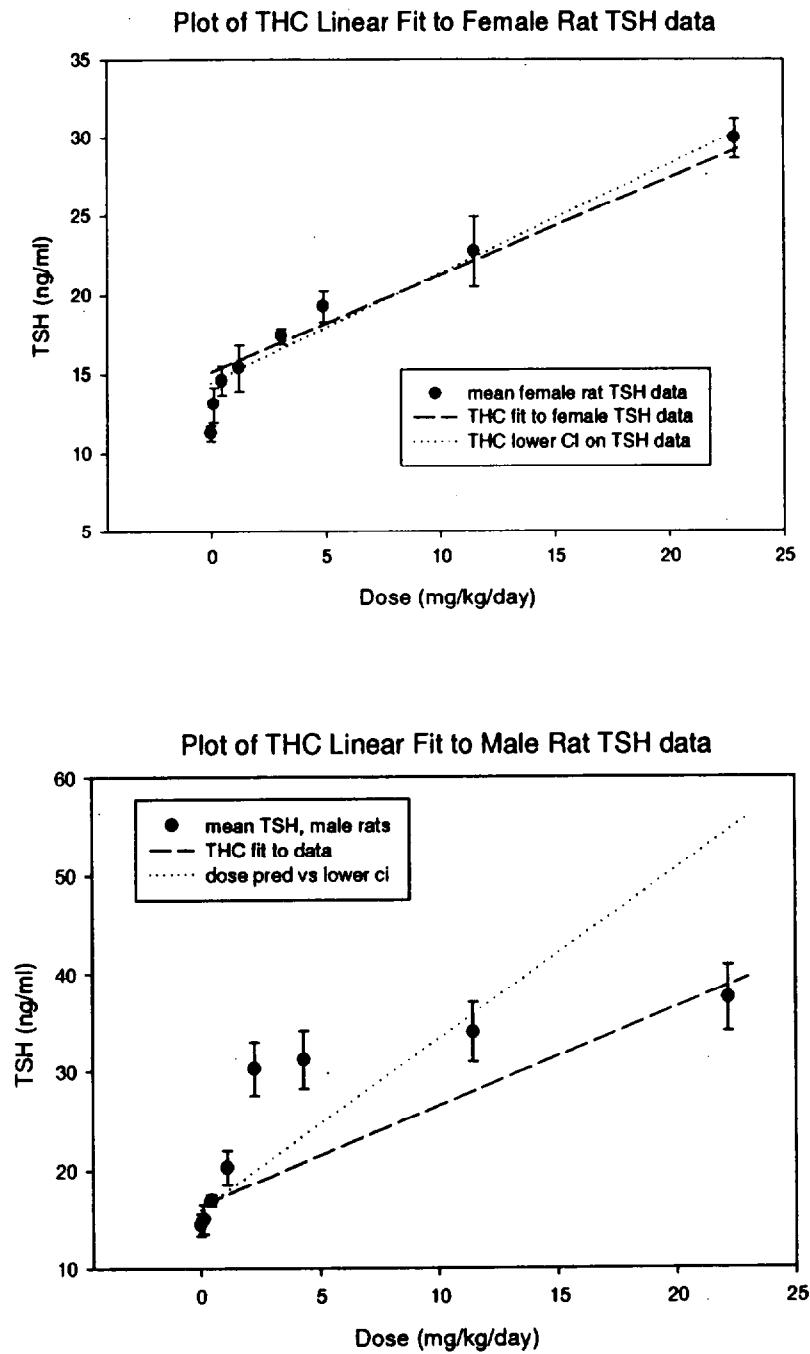


Figure A1-2. THC linear fits to TSH data from Caldwell Study. Fits are not statistically significant.

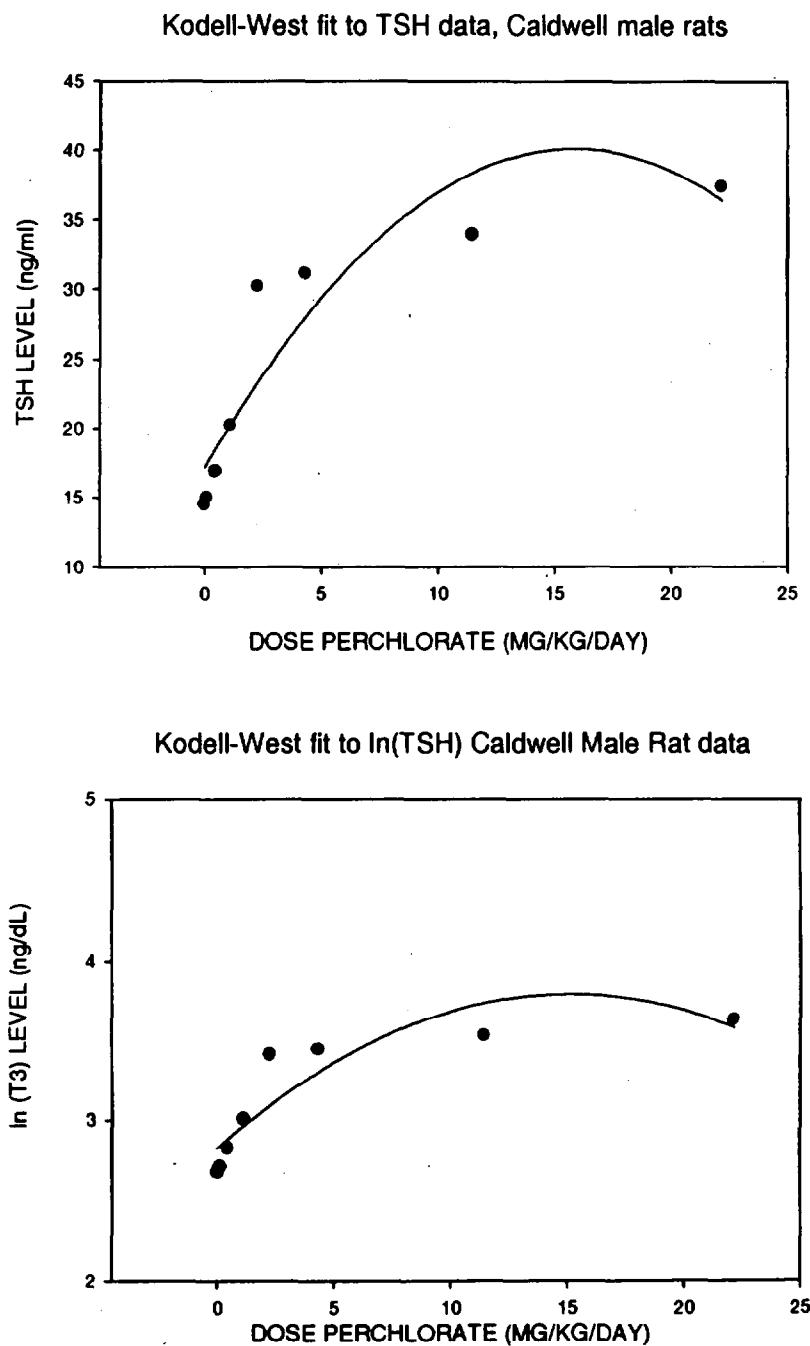


Figure A1-3. Quadratic fits to male TSH data. Fits are not statistically significant and contain a global maximum within the dose range tested (see pp. A1-9, A1-10).

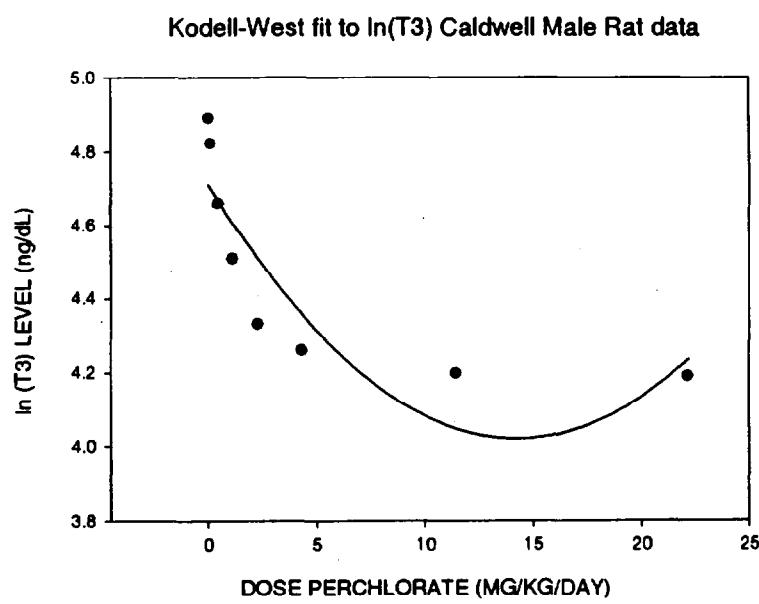
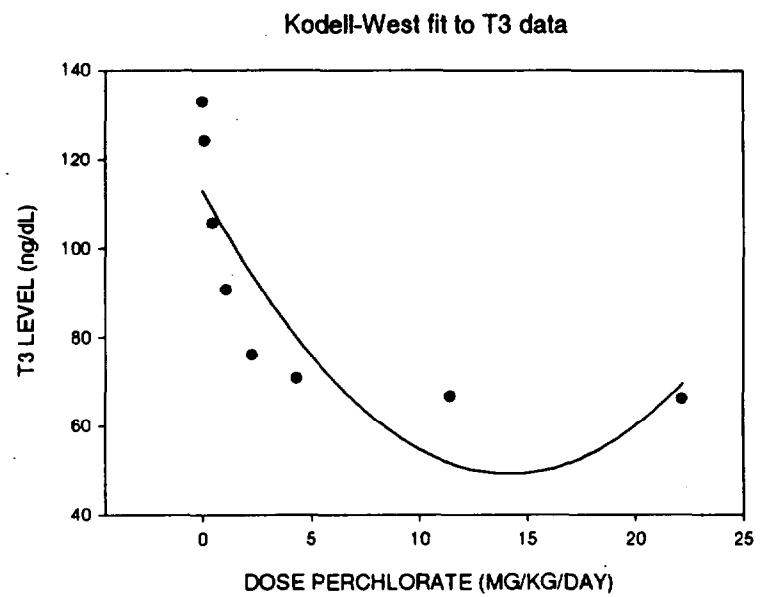


Figure A1-4. Quadratic fits to T3 data. Fits are not statistically significant and contain a global minimum within the dose range tested (see pp. A1-13, A1-14).

Kodell-West fit to T4 data, Caldwell male rats

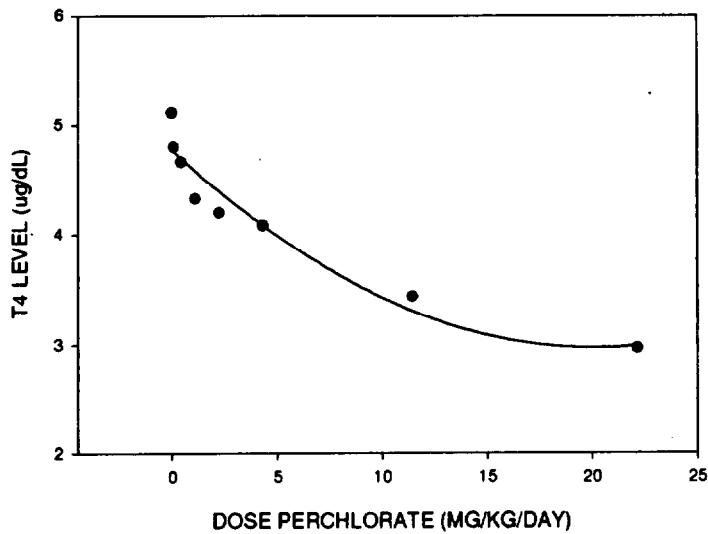
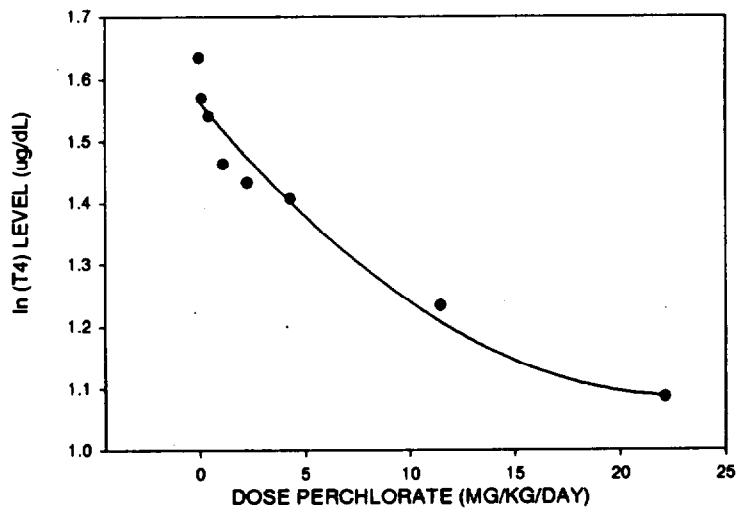
Kodell-West fit to $\ln(T4)$ Caldwell Male Rat data

Figure A1-5. Quadratic fits to T4 data. Fits are not statistically significant. Global minimum is at approximately the highest dose tested (see pp. A1-11, A1-12)

Caldwell male rat quadratic fits.

Polynomial Model male TSH
 Input Data File: CALDWELL.SET
 Mon Nov 16 09:37:59 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[\text{dose}] = \beta_0 + \beta_1 * \text{dose} + \beta_2 * \text{dose}^2$$

+ ...

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

Signs of the polynomial coefficients are not restricted

Total number of dose groups = 8

Total number of records with missing values = 0

Default Initial Parameter Values

var_const = 5.47044
 $\beta_0 = 17.1835$
 $\beta_1 = 2.8932$
 $\beta_2 = -0.0912862$

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	16.383	3.34417
β_0	17.1835	0.836158
β_1	2.8932	0.312542
β_2	-0.0912862	0.0142412

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	β_0	β_1	β_2
var_const	1	-3.2e-007	1.5e-007	
β_0	-3.2e-007	1	-0.62	0.51
β_1	1.5e-007	-0.62	1	-0.97
β_2	-1.7e-007	0.51	-0.97	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	6	14.476	1.153	17.184	16.383
0.1100	6	15.020	1.479	17.491	16.383
0.4400	6	16.917	0.531	18.399	16.383
1.1100	6	20.250	1.726	20.181	16.383
2.2600	6	30.233	2.736	23.050	16.383
4.3200	6	31.145	2.954	27.584	16.383
11.4400	6	33.960	3.061	37.290	16.383

22.1600 6 37.443 3.377 34.446 16.383

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma^2$

Model A2: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma_i^2$

Model R: $Y_i = \mu + e_i$
 $\text{Var}\{e_i\} = \sigma^2$

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-60.408916	9	-69.408916
A2	-48.855883	16	-64.855883
fitted	-91.109919	4	-95.109919
R	-198.386903	2	-200.386903

Test 1: Does response and/or variances differ among dose levels

(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test -2*log(Likelihood Ratio) p-value

Test 1	275.956	<.00001
Test 2	23.1061	0.001634
Test 3	61.402	<.00001

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

The p-value for Test 2 is less than .05. Variances may not be homogeneous

The p-value for Test 3 is less than .05. You may want to try a different model

Benchmark Dose Computation

Specified effect = 1.440000

Risk Type = Added response

Confidence level = 0.950000

BMD = 0.505791

BMDL = 0.428041

Polynomial Model male ln(TSH)
 Input Data File: CALDMAELN.SET
 Mon Nov 16 08:57:06 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[\text{dose}] = \beta_0 + \beta_1 * \text{dose} + \beta_2 * \text{dose}^2$$

+ ...

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0.

Signs of the polynomial coefficients are not restricted

Total number of dose groups = 8

Total number of records with missing values = 0

Default Initial Parameter Values

var_const = 0.00757925

$\beta_0 = 2.82466$

$\beta_1 = 0.126942$

$\beta_2 = -0.0042024$

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.0324555	0.00662496
β_0	2.82466	0.0372165
β_1	0.126942	0.0139109
β_2	-0.0042024	0.000633858

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	β_0	β_1	β_2
var_const	1	5.9e-009	-8.3e-009	
β_0	5.9e-009	1	-0.62	0.51
β_1	-8.3e-009	-0.62	1	-0.97
β_2	8.4e-009	0.51	-0.97	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	6	2.670	0.076	2.825	0.032
0.1100	6	2.705	0.104	2.838	0.032
0.4400	6	2.828	0.031	2.878	0.032
1.1100	6	3.005	0.084	2.956	0.032
2.2600	6	3.405	0.094	3.081	0.032
4.3200	6	3.434	0.103	3.276	0.032

11.4400	6	3.522	0.094	3.679	0.032
22.1600	6	3.620	0.088	3.481	0.032

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma^2$

Model A2: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma_i^2$

Model R: $Y_i = \mu + e_i$
 $\text{Var}\{e_i\} = \sigma^2$

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	97.551902	9	88.551902
A2	101.716469	16	85.716469
fitted	58.269234	4	54.269234
R	-40.249217	2	-42.249217

Test 1: Does response and/or variances differ among dose levels
 (A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test $-2 \log(\text{Likelihood Ratio})$ p-value

Test 1	275.602	<.00001
Test 2	8.32913	0.3045
Test 3	78.5653	<.00001

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

The p-value for Test 3 is less than .05. You may want to try a different model

Benchmark Dose Computation

Specified effect = 0.105300

Risk Type = Added response

Confidence level = 0.950000

BMD = 0.853633

BMDL = 0.719111

=====

Polynomial Model T4 male

Input Data File: CALDWELL.SET

Mon Nov 16 09:31:10 1998
 =====

BMDS MODEL RUN

The form of the response function is:

$$Y[\text{dose}] = \beta_0 + \beta_1 * \text{dose} + \beta_2 * \text{dose}^2$$

+ ...

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

Signs of the polynomial coefficients are not restricted

Total number of dose groups = 8

Total number of records with missing values = 0

Default Initial Parameter Values

var_const = 0.0314518

beta_0 = 4.77351

beta_1 = -0.179646

beta_2 = 0.00447551

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.0573971	0.0117161
beta_0	4.77351	0.0494921
beta_1	-0.179646	0.0184993
beta_2	0.00447551	0.000842932

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	beta_0	beta_1	beta_2
var_const	1	5.1e-006	-2.7e-007	
	5.1e-006	1	-0.62	0.51
	-2.7e-007	-0.62	1	-0.97
	9.2e-008	0.51	-0.97	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	6	5.123	0.201	4.774	0.057
0.1100	6	4.803	0.079	4.754	0.057
0.4400	6	4.662	0.087	4.697	0.057
1.1100	6	4.320	0.217	4.585	0.057
2.2600	6	4.190	0.075	4.400	0.057

4.3200	6	4.082	0.186	4.100	0.057
11.4400	6	3.428	0.242	3.355	0.057
22.1600	6	2.960	0.227	3.089	0.057

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma^2$

Model A2: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma_i^2$

Model R: $Y_i = \mu + e_i$
 $\text{Var}\{e_i\} = \sigma^2$

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	63.398933	9	54.398933
A2	72.093886	16	56.093886
fitted	44.586256	4	40.586256
R	-75.545665	2	-77.545665

Test 1: Does response and/or variances differ among dose levels

(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	p-value
Test 1	277.889	<.00001
Test 2	17.3899	0.01505
Test 3	37.6254	<.00001

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

The p-value for Test 2 is less than .05. Variances may not be homogeneous

The p-value for Test 3 is less than .05. You may want to try a different model

Benchmark Dose Computation

Specified effect = 0.510000

Risk Type = Added response

Confidence level = 0.950000

BMD = 3.074381

BMDL = 2.610702

Polynomial Model of ln(T4), male Caldwell
 Input Data File: CALDMALEN.SET
 Mon Nov 16 08:50:01 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[\text{dose}] = \beta_0 + \beta_1 \cdot \text{dose} + \beta_2 \cdot \text{dose}^2 \\ + \dots$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

Signs of the polynomial coefficients are not restricted

Total number of dose groups = 8

Total number of records with missing values = 0

Default Initial Parameter Values

var_const = 0.00225512

$\beta_0 = 1.56293$

$\beta_1 = -0.0414219$

$\beta_2 = 0.00090346$

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.00318547	0.000650232
β_0	1.56293	0.0116595
β_1	-0.0414219	0.00435811
β_2	0.000903463	0.00019858

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	β_0	β_1	β_2
var_const	1	1.3e-006	-2.2e-006	
β_0	1.3e-006	1	-0.62	0.51
β_1	-2.2e-006	-0.62	1	-0.97
β_2	2.3e-006	0.51	-0.97	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	6	1.633	0.039	1.563	0.003
0.1100	6	1.569	0.017	1.558	0.003
0.4400	6	1.539	0.019	1.545	0.003
1.1100	6	1.462	0.052	1.519	0.003

2.2600	6	1.433	0.018	1.476	0.003
4.3200	6	1.406	0.045	1.405	0.003
11.4400	6	1.230	0.071	1.218	0.003
22.1600	6	1.083	0.076	1.109	0.003

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma^2$

Model A2: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma_i^2$

Model R: $Y_i = \mu + e_i$
 $\text{Var}\{e_i\} = \sigma^2$
 Likelihoods of Interest

Model	Log(Likelihood)	DF	AIC
A1	126.644914	9	117.644914
A2	139.850540	16	123.850540
fitted	113.979686	4	109.979686
R	57.163480	2	55.163480

Test 1: Does response and/or variances differ among dose levels
 (A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test -2*log(Likelihood Ratio) p-value

Test 1	138.963	<.00001
Test 2	26.4113	0.0004252
Test 3	25.3305	0.0001203

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

The p-value for Test 2 is less than .05. Variances may not be homogeneous

The p-value for Test 3 is less than .05. You may want to try a different model

Benchmark Dose Computation

Specified effect = 0.105300

Risk Type = Added response

Confidence level = 0.950000

BMD = 2.701288

BMDL = 2.293879

 Polynomial Model of T3 male
 Input Data File: CALDWELL.SET
 Mon Nov 16 09:34:52 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[\text{dose}] = \beta_0 + \beta_1 \cdot \text{dose} + \beta_2 \cdot \text{dose}^2$$

+ ...

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

Signs of the polynomial coefficients are not restricted

Total number of dose groups = 8

Total number of records with missing values = 0

Default Initial Parameter Values

var_const = 63.2234

$\beta_0 = 112.818$

$\beta_1 = -9.00346$

$\beta_2 = 0.317817$

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	227.04	46.3443
β_0	112.818	3.11274
β_1	-9.00346	1.16349
β_2	0.317817	0.053015

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	β_0	β_1	β_2
var_const	1	8.1e-009	-1.5e-009	
		-7.7e-010		
β_0	8.1e-009	1	-0.62	0.51
β_1	-1.5e-009	-0.62	1	-0.97
β_2	-7.7e-010	0.51	-0.97	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	6	132.865	11.711	112.818	227.040
0.1100	6	124.018	11.945	111.867	227.040
0.4400	6	105.667	6.601	109.058	227.040
1.1100	6	90.460	8.439	103.569	227.040
2.2600	6	75.415	6.074	94.812	227.040
4.3200	6	70.692	5.905	81.227	227.040
11.4400	6	66.463	3.664	55.048	227.040
22.1600	6	65.935	5.097	76.413	227.040

Model Descriptions for likelihoods calculated

$$\text{Model A1: } Y_{ij} = \mu_i + e_{ij}$$

$$\text{Var}\{e_{ij}\} = \sigma^2$$

$$\text{Model A2: } Y_{ij} = \mu_i + e_{ij}$$

$$\text{Var}\{e_{ij}\} = \sigma_i^2$$

$$\text{Model R: } Y_i = \mu_i + e_i$$

$$\text{Var}\{e_i\} = \sigma^2$$

Likelihoods of Interest

Model	Log(Likelihood)	DF	AIC
A1	-119.144474	9	-128.144474
A2	-112.431987	16	-128.431987
fitted	-154.203021	4	-158.203021
R	-249.600721	2	-251.600721

Test 1: Does response and/or variances differ among dose levels

(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

$$\text{Test } -2 \cdot \log(\text{Likelihood Ratio}) \quad \text{p-value}$$

Test 1	260.912	<.00001
Test 2	13.425	0.06241
Test 3	70.1171	<.00001

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

The p-value for Test 3 is less than .05. You may want to try a different model

Benchmark Dose Computation

Specified effect = 13.280000

Risk Type = Added response

Confidence level = 0.950000

BMD = 1.561003

BMDL = 1.272751

 Polynomial Model male ln(T3)
 Input Data File: CALDMAELN.SET
 Mon Nov 16 08:54:14 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[\text{dose}] = \beta_0 + \beta_1 \cdot \text{dose} + \beta_2 \cdot \text{dose}^2$$

+ ...

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

Signs of the polynomial coefficients are not restricted

Total number of dose groups = 8

Total number of records with missing values = 0

Default Initial Parameter Values

var_const = 0.00669075

 $\beta_0 = 4.71139$ $\beta_1 = -0.0970158$ $\beta_2 = 0.00337791$

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.0212411	0.00433582
β_0	4.71139	0.0301078
β_1	-0.0970158	0.0112538
β_2	0.00337791	0.000512786

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	β_0	β_1	β_2
var_const	1	1.9e-008	-3.4e-008	
β_0	1.9e-008	1	-0.62	0.51
β_1	-3.4e-008	-0.62	1	-0.97
β_2	3.4e-008	0.51	-0.97	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	6	4.886	0.094	4.711	0.021
0.1100	6	4.816	0.099	4.701	0.021
0.4400	6	4.659	0.063	4.671	0.021
1.1100	6	4.501	0.094	4.612	0.021
2.2600	6	4.320	0.079	4.517	0.021

4.3200	6	4.255	0.083	4.370	0.021
11.4400	6	4.195	0.055	4.082	0.021
22.1600	6	4.186	0.077	4.295	0.021

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma^2$

Model A2: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma_i^2$

Model R: $Y_i = \mu + e_i$
 $\text{Var}\{e_i\} = \sigma^2$

Likelihoods of Interest

Model	Log(Likelihood)	DF	AIC
A1	100.544421	9	91.544421
A2	102.162344	16	86.162344
fitted	68.443599	4	64.443599
R	-19.201291	2	-21.201291

Test 1: Does response and/or variances differ among dose levels
 (A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test -2*log(Likelihood Ratio) p-value

Test 1	239.491	<.00001
Test 2	3.23585	0.8624
Test 3	64.2016	<.00001

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

The p-value for Test 3 is less than .05. You may want to try a different model

Benchmark Dose Computation

Specified effect = 0.105300

Risk Type = Added response

Confidence level = 0.950000

BMD = 1.129836

BMDL = 0.941957

Appendix A2. BMDs calculated for Caldwell 14-day rat study.

Table A2-1 – USEPA BMD Power Function fits to Caldwell combined male and female data.....	A2-2
Table A2-2 -- BMDLs from Caldwell, Male and Female combined. BMRs at CTL - 10%, 20%, 40% of CTL.....	A2-3
Output from USEPA BMD program.....	A2- 4
TSH, male and female.....	A2-4
ln TSH, male and female.....	A2-5
TSH, female.....	A2-6
ln TSH, female.....	A2-7
T3, male and female.....	A2-8
ln T3, male and female.....	A2-9
T4, male and female.....	A2-10
ln T4, male and female.....	A2-11

Figures of the above fits.

Table A2-1 – USEPA BMD Power Function fits to Caldwell combined male and female data.
Benchmark response set at 10% less than control.

Endpoint	p of fit	BMD	BMDL	NOAEL/ LOAEL	BMD: N(L)OAEL	BMDL: N(L)OAEL	BMR: 10% CTL SD
TSH [†]	0.272	0.014	0.0002	0.44	0.032	4.55e-4	1.29 1.88
ln TSH [†]	0.099	0.017	0.002	0.44	0.039	4.55e-3	-.1053
female TSH ^{††}	0.077	0.19	0.032	0.1	1.90	0.32	1.125 0.48
female ln(TSH) [†]	0.50	0.078	0.035	0.1	0.78	0.35	-.1053
male TSH	no significant fits to male TSH or male ln(TSH) data						
T3 [†]	0.107	0.00035	0.00	0.1*	0.0035	NA	13.07 10.21
lnT3 [†]	0.091	0.0004	2e-6	0.1*	0.004	2.00e-5	-.1053
T4 [†]	0.303	0.243	0.096	0.1*	2.43	0.96*	0.506 0.321
ln (T4) [†]	0.172	0.340	0.0997	0.1*	3.40	1.00*	-.1053

* LOAEL; otherwise, value is NOAEL.

† Unrestricted quadratic: fit non-monotonic, not significant.

Restricted polynomial (linear): fit not significant

‡ Unrestricted quadratic: fit not significant, global minimum at approx. high dose

Restricted polynomial (linear): fit not significant

†† Unrestricted quadratic: fit monotonic but not significant

Restricted polynomial (linear): fit not significant

Table A2-2 -- BMDLs from Caldwell, Male and Female combined. BMRs at CTL - 10%, 20%, 40% of CTL.

	p of fit	-10%	-20%	-40%	mean	NOAEL	
TSH	0.272	0.0002	0.0038	0.0604	12.861	0.44	power fcn fit
ln(TSH)	0.099	0.002	0.043	1.11		0.44	power fcn fit
T3	.0108	0.00	0.000036	0.042*	130.69	0.10**	power fcn fit
ln(T3)	0.091	0.000002	0.000642	0.478		0.10**	powerfcn fit
T4	0.303	0.096	1.299	16.78	5.06	0.10**	power fcn fit
ln(T4)	0.172	0.100	1.213	16.89		0.10**	power fcn fit

*BMDL calculation failed at some values. This means BMDL value may not be accurate.

**LOAEL not NOAEL.

Output files from USEPA BMD PROGRAM

Caldwell thyroid data

Power Model of TSH. male and Female
combined; BMR: 0.90 Ctl
Input Data File: CALDALL.SET
Tue Nov 10 08:29:26 1998

BMDS MODEL RUN

The form of the response function is:
 $Y[\text{dose}] = \text{control} + \text{slope} * \text{dose}^{\text{power}}$
 Dependent variable = MEAN
 Independent variable = dose
 var_power is set to 0
 The sign of the slope is not restricted

Total number of dose groups = 8
 Total number of records with missing values = 0
 HERE is the pooled variance 19.1901

Default Initial Parameter Values
 var_const = 20.9346
 control = 12.861
 slope = 4.60069
 power = 0.548814

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	20.5066	2.96183
control	12.0139	0.795724
slope	6.67556	0.472319
power	0.383691	0.0431575

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	control	slope	power
var_const	1	-0.0067	0.012	-0.036
control	-0.0067	1	-0.81	0.18
slope	0.012	-0.81	1	-0.33
power	-0.036	0.18	-0.33	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	12	12.861	1.882	12.014	20.507
0.1100	12	14.037	1.623	14.876	20.507
0.4500	12	15.751	1.412	16.928	20.507
1.1100	12	17.803	2.583	18.962	20.507
2.6300	12	23.810	6.966	21.688	20.507
4.6200	12	25.200	6.555	24.023	20.507

11.4500	12	28.433	6.310	29.025	20.507
22.5100	12	33.684	4.618	34.063	20.507

Model Descriptions for likelihoods calculated
 Model A1: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma^2$

Model A2: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma_i^2$

Model R: $Y_i = \mu_i + e_i$
 $\text{Var}\{e_i\} = \sigma^2$

Likelihoods of Interest

Model	Log(Likelihood)	DF	AIC
A1	-189.810838	9	-198.810838
A2	-159.070694	16	-175.070694
fitted	-192.995712	4	-196.995712
R	-312.551814	2	-314.551814

Test 1: Does response and/or variances differ among Dose levels
 (A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	p-value
Test 1	245.482	<.00001
Test 2	61.4803	<.00001
Test 3	6.36975	0.2719

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

The p-value for Test 2 is less than .05. Variances may not be homogeneous

Benchmark Dose Computation

Specified effect = 1.290000
 Risk Type = Added response
 Confidence level = 0.950000
 BMD = 0.013785
 BMDL = 0.000231

Power Model ln(TSH) BMR 0.90 CTL
 Input Data File: LNCALDALL.SET
 Tue Nov 10 09:13:09 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[dose] = control + slope * dose^{power}$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

The sign of the slope is not restricted

Total number of dose groups = 8

Total number of records with missing values = 0

HERE is the pooled variance 0.0335047

Default Initial Parameter Values

var_const	=	0.0365506
control	=	2.545
slope	=	0.292075
power	=	0.444959

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.0369034	0.00533223
control	2.50693	0.0365289
slope	0.386221	0.0249875
power	0.316881	0.0366858

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	control	slope	power
var_const	1	-0.0086	0.014	-0.046
control	-0.0086	1	-0.84	0.19
slope	0.014	-0.84	1	-0.31
power	-0.046	0.19	-0.31	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est StdDev
0.0000	12	2.545	0.143	2.507	0.037
0.1100	12	2.636	0.117	2.699	0.037
0.4500	12	2.753	0.091	2.807	0.037
1.1100	12	2.866	0.163	2.906	0.037
2.4600	12	3.130	0.295	3.021	0.037
4.6200	12	3.196	0.261	3.134	0.037
11.4500	12	3.325	0.225	3.343	0.037
22.5300	12	3.509	0.133	3.543	0.037

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma^2$

Model A2: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma_i^2$

Model R: $Y_i = \mu + e_i$
 $\text{Var}\{e_i\} = \sigma^2$

Likelihoods of Interest

Model	Log(Likelihood)	DF	AIC
A1	115.011331	9	106.011331
A2	128.660760	16	112.660760
fitted	110.373724	4	106.373724
R	-35.112300	2	-37.112300

Test 1: Does response and/or variances differ among Dose levels

(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	p-value
Test 1	300.247	<.00001
Test 2	27.2989	0.0002944
Test 3	9.27521	0.09858

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

The p-value for Test 2 is less than .05. Variances may not be homogeneous

Benchmark Dose Computation

Specified effect = 0.105400 (0.90 CTL)

Risk Type = Added response

Confidence level = 0.950000

BMD = 0.016602

BMDL = 0.002172

Power Model female TSH. BMR 0.90 ctl
 Input Data File: CALDFEMTSH.SET
 Tue Nov 10 09:41:09 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[\text{dose}] = \text{control} + \text{slope} * \text{dose}^{\text{power}}$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

The sign of the slope is not restricted

Total number of dose groups = 8

Total number of records with missing values = 0

HERE is the pooled variance 1.26555

Default Initial Parameter Values

var_const	=	1.51866
control	=	11.25
slope	=	4.21433
power	=	0.427013

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	1.55719	0.318445
control	11.9357	0.266136
slope	2.91696	0.09912
power	0.571731	0.0265214

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	control	slope	power
var_const	1	0.0084	-0.02	0.061
control	0.0084	1	-0.73	0.14
slope	-0.02	-0.73	1	-0.33
power	0.061	0.14	-0.33	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	6	11.250	0.480	11.936	1.557
0.1200	6	13.050	1.130	12.804	1.557
0.4700	6	14.580	0.920	13.830	1.557
1.2300	6	15.360	1.450	15.219	1.557
3.0600	6	17.380	0.510	17.465	1.557

4.9100	6	19.250	0.990	19.181	1.557
11.4700	6	22.740	2.200	23.704	1.557
22.8600	6	29.920	1.270	29.392	1.557

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma^2$

Model A2: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma_i^2$

Model R: $Y_i = \mu + e_i$
 $\text{Var}\{e_i\} = \sigma^2$

Likelihoods of Interest

Model	Log(Likelihood)	DF	AIC
A1	-29.652203	9	-38.652203
A2	-19.747341	16	-35.747341
fitted	-34.629194	4	-38.629194
R	-634.615738	2	-636.615738

Test 1: Does response and/or variances differ among Dose levels

(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test -2*log(Likelihood Ratio) p-value

Test 1	1209.93	<.00001
Test 2	19.8097	0.005996
Test 3	9.95398	0.07655

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

The p-value for Test 2 is less than .05. Variances may not be homogeneous

Benchmark Dose Computation

Specified effect = 1.125000 (0.90 CTL)

Risk Type = Added response

Confidence level = 0.950000

BMD = 0.188916

BMDL = 0.032025

Power Model female ln(TSH) BMR 0.90 CTL
 Input Data File: CALDFEMTSH.SET
 Tue Nov 10 09:53:39 1998

	4.9100	6	2.957	0.051	2.954	0.004
11.4700	6	3.128	0.095	3.156	0.004	
22.8600	6	3.398	0.044	3.377	0.004	

Model Descriptions for likelihoods calculated

BMDS MODEL RUN

The form of the response function is:

$$Y[dose] = control + slope * dose^{power}$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

The sign of the slope is not restricted

Total number of dose groups = 8

Total number of records with missing values = 0

HERE is the pooled variance 0.00393552

Default Initial Parameter Values

var_const = 0.00472262

control = 2.419

slope = 0.308949

power = 0.349524

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.00430805	0.000880117
control	2.43272	0.0164732
slope	0.282509	0.00966866
power	0.385545	0.0223927

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	control	slope	power
var_const	1	0.0078	-0.014	0.041
control	0.0078	1	-0.81	0.19
slope	-0.014	-0.81	1	-0.35
power	0.041	0.19	-0.35	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	6	2.419	0.042	2.433	0.004
0.1200	6	2.566	0.087	2.557	0.004
0.4700	6	2.678	0.062	2.644	0.004
1.2300	6	2.727	0.101	2.739	0.004
3.0600	6	2.855	0.029	2.868	0.004

Model A1: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma^2$

Model A2: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma_i^2$

Model R: $Y_i = \mu + e_i$
 $\text{Var}\{e_i\} = \sigma^2$

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	108.905089	9	99.905089
A2	116.449847	16	100.449847
fitted	106.734425	4	102.734425
R	-424.348853	2	-426.348853

Test 1: Does response and/or variances differ among Dose levels
 (A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	p-value
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Test 1	1066.51	<.00001
Test 2	15.0895	0.03487
Test 3	4.34133	0.5014

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

The p-value for Test 2 is less than .05. Variances may not be homogeneous

Benchmark Dose Computation

Specified effect = 0.105300 (0.90 CTL)

Risk Type = Added response

Confidence level = 0.950000

BMD = 0.077324

BMDL = 0.034563

Power Model
 Input Data File: CALDALL.SET
 T3, male and female combined, BMR: 0.90(ctl)
 Tue Nov 10 08:10:10 1998

BMDS MODEL RUN

The form of the response function is:

$Y[\text{dose}] = \text{control} + \text{slope} * \text{dose}^{\text{power}}$
 Dependent variable = MEAN
 Independent variable = dose
 var_power is set to 0
 The sign of the slope is not restricted
 Total number of dose groups = 8
 Total number of records with missing values = 0
 HERE is the pooled variance 108.427

Default Initial Parameter Values

var_const = 118.284
 control = 130.688
 slope = -41.818
 power = 0.175039

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	119.125	17.1993
control	131.378	2.67465
slope	-43.6838	2.42581
power	0.151624	0.0291779

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	control	slope	power
var_const	1	0.0031	-0.0046	-0.024
control	0.0031	1	-0.91	-0.13
slope	-0.0046	-0.91	1	0.19
power	-0.024	-0.13	0.19	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	12	130.688	10.208	131.378	119.125
0.1100	12	104.308	22.466	100.119	119.125
0.4500	12	94.870	12.882	92.676	119.125
1.1100	12	85.569	9.076	86.997	119.125
2.6300	12	77.358	6.326	80.796	119.125
4.6200	12	71.276	4.348	76.285	119.125
11.4500	12	67.505	3.546	68.157	119.125
22.5100	12	66.168	4.187	61.334	119.125

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma^2$

Model A2: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma_i^2$

Model R: $Y_i = \mu_i + e_i$
 $\text{Var}\{e_i\} = \sigma^2$

Likelihoods of Interest

Model	Log(Likelihood)	DF	AIC
A1	-272.931732	9	-281.931732
A2	-238.329391	16	-254.329391
fitted	-277.448408	4	-281.448408
R	-462.518331	2	-464.518331

Test 1: Does response and/or variances differ among Dose levels

(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	p-value
Test 1	379.173	<.00001
Test 2	69.2047	<.00001
Test 3	9.03335	0.1077

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

The p-value for Test 2 is less than .05. Variances may not be homogeneous

Benchmark Dose Computation

Specified effect = 13.070000

Risk Type = Added response

Confidence level = 0.950000

BMD = 0.000350

BMDL = 0.000000

BMDL curve computation failed for BMR = -8.065000.
 The BMDL curve appearing in the graph may not be accurate.

Power Model ln(T3); BMR: 0.90 CTL
Input Data File: LNCALDALL.SET
Tue Nov 10 09:05:39 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[\text{dose}] = \text{control} + \text{slope} * \text{dose}^{\text{power}}$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

The sign of the slope is not restricted

Total number of dose groups = 8

Total number of records with missing values = 0

HERE is the pooled variance 0.0113747

Default Initial Parameter Values

var_const = 0.0124087
control = 4.87
slope = -0.402071
power = 0.204881

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.0125576	0.00181324
control	4.87892	0.0262773
slope	-0.424104	0.0229584
power	0.178349	0.0285886

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	control	slope	power
var_const	1	0.0042	-0.0062	-0.028
control	0.0042	1	-0.9	-0.15
slope	-0.0062	-0.9	1	0.22
power	-0.028	-0.15	0.22	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	12	4.870	0.081	4.879	0.013
0.1100	12	4.626	0.215	4.593	0.013
0.4500	12	4.544	0.136	4.511	0.013
1.1100	12	4.445	0.105	4.447	0.013
2.4600	12	4.345	0.081	4.381	0.013
4.6200	12	4.265	0.061	4.322	0.013
11.4500	12	4.211	0.053	4.224	0.013
22.5300	12	4.190	0.063	4.140	0.013

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma^2$

Model A2: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma_i^2$

Model R: $Y_i = \mu + e_i$
 $\text{Var}\{e_i\} = \sigma^2$

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	166.865582	9	157.865582
A2	187.985866	16	171.985866
fitted	162.116666	4	158.116666
R	-36.141269	2	-38.141269

Test 1: Does response and/or variances differ among Dose levels
(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	p-value
Test 1	406.014	<.00001
Test 2	42.2406	<.00001
Test 3	9.49783	0.09078

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

The p-value for Test 2 is less than .05. Variances may not be homogeneous

Benchmark Dose Computation

Specified effect = 0.105400 (0.90 CTL)

Risk Type = Added response

Confidence level = 0.950000

BMD = 0.000407

BMDL = 0.000002

Power Model of T4. BMR: 0.90(Ctl)
Input Data File: CALDALL.SET
Tue Nov 10 07:52:05 1998

BMDS MODEL RUN

The form of the response function is:

$Y[\text{dose}] = \text{control} + \text{slope} * \text{dose}^{\text{power}}$
Dependent variable = MEAN
Independent variable = dose
var_power is set to 0

The sign of the slope is not restricted

Total number of dose groups = 8
Total number of records with missing values = 0
HERE is the pooled variance 0.0636325

Default Initial Parameter Values

var_const = 0.0694173
control = 5.06
slope = -0.837014
power = 0.281552

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.0677599	0.00978402
control	5.03208	0.0503272
slope	-0.783756	0.0351681
power	0.309493	0.0283924

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	control	slope	power
var_const	1	-0.0058	0.0094	0.028
control	-0.0058	1	-0.85	-0.21
slope	0.0094	-0.85	1	0.34
power	0.028	-0.21	0.34	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	12	5.060	0.321	5.032	0.068
0.1100	12	4.605	0.246	4.636	0.068
0.4500	12	4.391	0.292	4.420	0.068
1.1100	12	4.135	0.272	4.223	0.068
2.6300	12	4.023	0.208	3.975	0.068
4.6200	12	3.909	0.242	3.773	0.068
11.4500	12	3.338	0.264	3.365	0.068
22.5100	12	2.941	0.247	2.977	0.068

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu_i + e_{ij}$

$\text{Var}\{e_{ij}\} = \sigma^2$

Model A2: $Y_{ij} = \mu_i + e_{ij}$

$\text{Var}\{e_{ij}\} = \sigma_i^2$

Model R: $Y_i = \mu + e_i$

$\text{Var}\{e_i\} = \sigma^2$

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	84.222300	9	75.222300
A2	85.667352	16	69.667352
fitted	81.205658	4	77.205658
R	-218.365203	2	-220.365203

Test 1: Does response and/or variances differ among Dose levels
(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	p-value
Test 1	605.175	<.00001
Test 2	2.8901	0.895
Test 3	6.03328	0.303

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

Benchmark Dose Computation

Specified effect = 0.506000

Risk Type = Added response

Confidence level = 0.950000

BMD = 0.243217

BMDL = 0.095548

Power Model ln(t4), male and female, BMR:
 0.90(ctl)
 Input Data File: LNCALDALL.SET
 Tue Nov 10 08:54:05 1998

BMDS MODEL RUN

The form of the response function is:
 $Y[\text{dose}] = \text{control} + \text{slope} * \text{dose}^{\text{power}}$
 Dependent variable = MEAN
 Independent variable = dose
 var_power is set to 0
 The sign of the slope is not restricted

Total number of dose groups = 8
 Total number of records with missing values = 0
 HERE is the pooled variance 0.00416243

Default Initial Parameter Values
 var_const = 0.00454083
 control = 1.62
 slope = -0.183859
 power = 0.320497

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.00451131	0.000651715
control	1.60674	0.0118715
slope	-0.158904	0.00717307
power	0.380438	0.030294

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	control	slope	power
var_const	1	-0.0086	0.015	0.042
control	-0.0086	1	-0.81	-0.21
slope	0.015	-0.81	1	0.36
power	0.042	-0.21	0.36	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	12	1.620	0.065	1.607	0.005
0.1100	12	1.526	0.054	1.538	0.005
0.4500	12	1.478	0.067	1.489	0.005
1.1100	12	1.418	0.066	1.441	0.005
2.4600	12	1.391	0.052	1.383	0.005
4.6200	12	1.362	0.062	1.322	0.005
11.4500	12	1.203	0.081	1.205	0.005
22.5300	12	1.075	0.085	1.087	0.005

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu(i) + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma^2$

Model A2: $Y_{ij} = \mu(i) + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma^2(i)$

Model R: $Y_i = \mu + e_i$
 $\text{Var}\{e_i\} = \sigma^2$

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	215.119502	9	206.119502
A2	217.644603	16	201.644603
fitted	211.256008	4	207.256008
R	-94.257788	2	-96.257788

Test 1: Does response and/or variances differ among Dose levels
 (A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

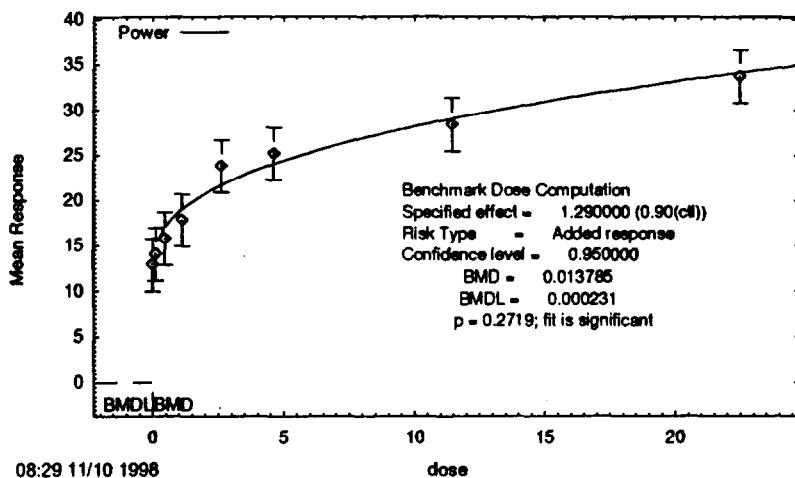
Test	-2*log(Likelihood Ratio)	p-value
Test 1	618.755	<.00001
Test 2	5.0502	0.6538
Test 3	7.72699	0.1719

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

Benchmark Dose Computation
 Specified effect = 0.105400 (.90(ctl))
 Risk Type = Added response
 Confidence level = 0.950000
 BMD = 0.339895
 BMDL = 0.099681

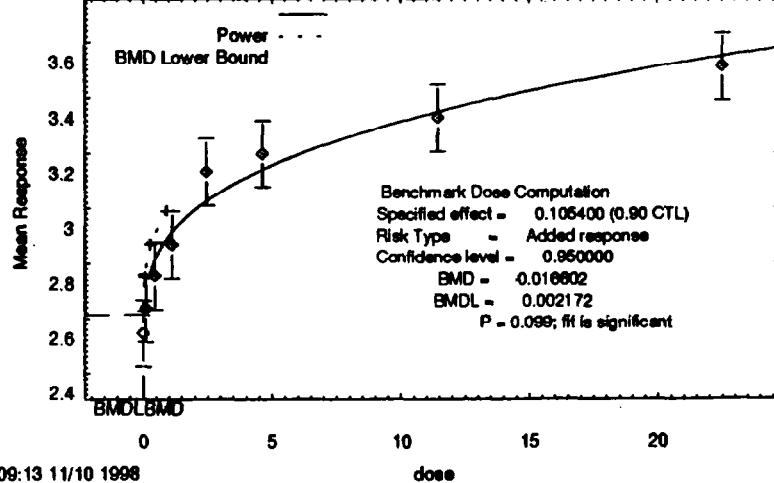
TSH BMD Calculation, Caldwell Male and Female Data

Power Model with 0.95 Confidence Level

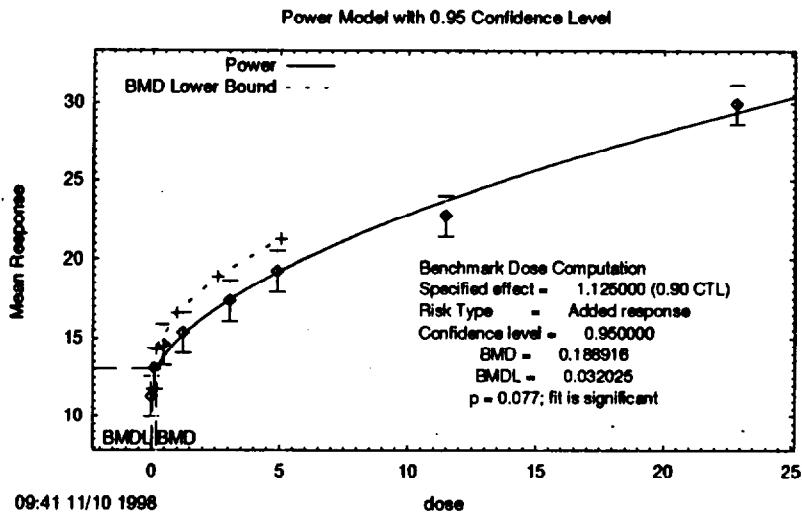


In(TSH) BMD Calculation, Caldwell Male and Female Data

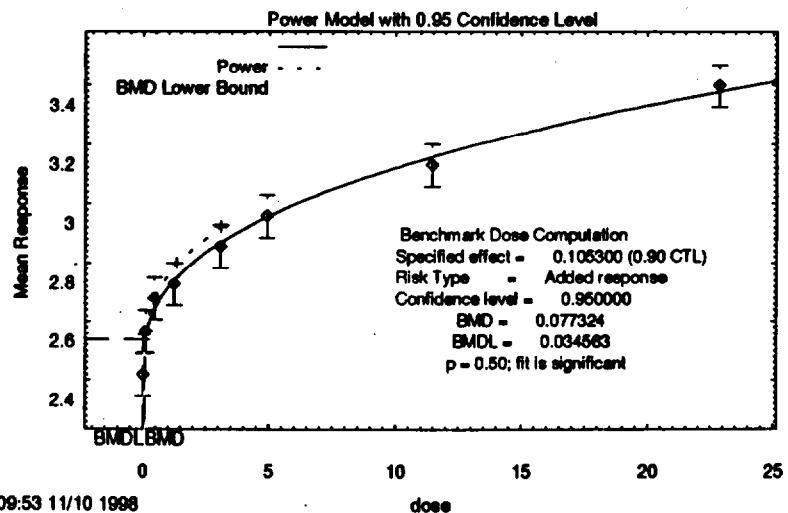
Power Model with 0.95 Confidence Level



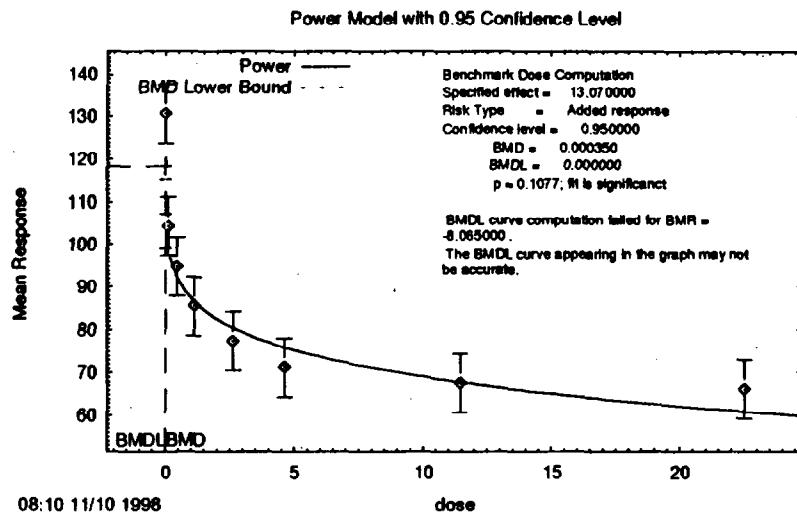
TSH BMD Calculation, Caldwell Female Data



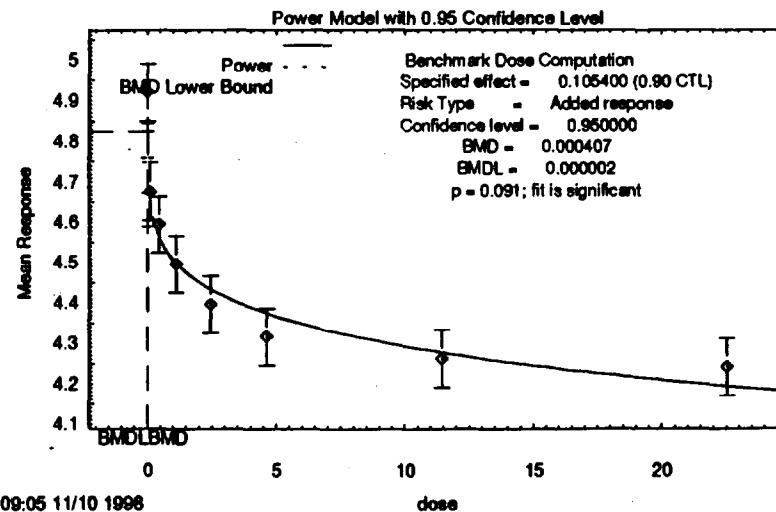
In(TSH) BMD Calculation, Caldwell Female Data



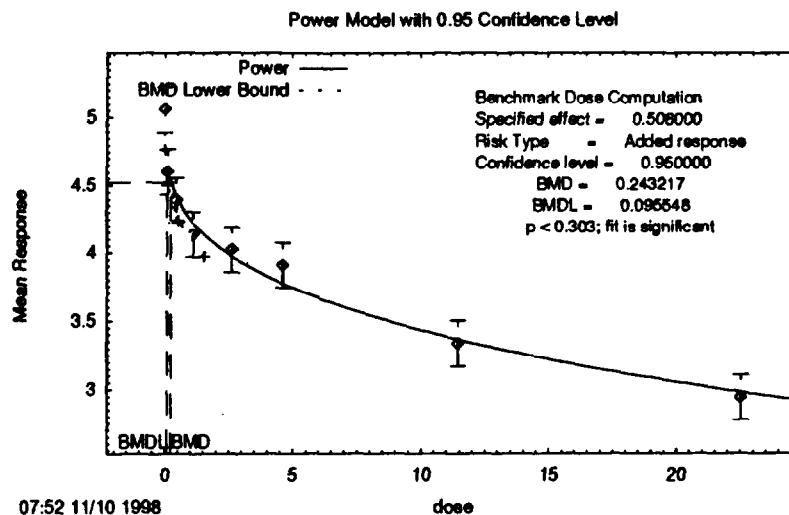
T3 BMD Calculation, Caldwell Male and Female Data



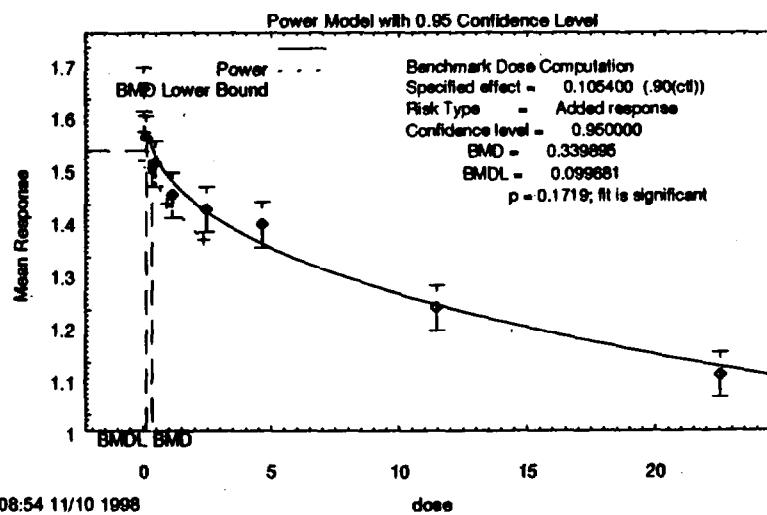
In(T3) BMD Calculation, Caldwell Male and Female Data



T4 BMD Calculation, Caldwell Male and Female Data



In(T4) BMD Calculation, Caldwell Male and Female Data



Appendix A3. BMDs calculated for Subchronic Study, 14 and 90 day time points

Table A3-1 – USEPA BMDs from Power Function fits to 90 day study, 14 day time point, male and female rats combined.	A3-2
Table A3-2 – BMDLs from Subchronic Study, 14 day time point, male and female combined. BMRs at CTL - 10%, 20%, 40% of CTL.....	A3-3
Table A3-3 – USEPA BMDs from fits to Subchronic study, 90 day time point, male and female rats combined. BMR set at 10% less than control.....	A3-4
Table A3-4 – BMDLs from Subchronic Study, 90 day time point, male and female combined. BMRs at CTL - 10%, 20%, 40% of CTL.....	A3-4
Subchronic (90 day study): 14 Day Time point	A3-5
Power Model TSH	A3-5
Polynomial Model TSH*	A3-6
Power Model on ln (TSH)	A3-7
Power Model of T3	A3-8
Power Model of ln(T3)	A3-9
Power Model of T4	A3-10
Polynomial Model of T4	A3-11
Power Model of ln(T4)	A3-12
Polynomial Model of ln(T4)	A3-13
Subchronic (90 day study): 90 Day Time point	A3-14
Power Model of TSH	A3-14
Power Model ln(TSH)	A3-15
Power Model of T3	A3-16
Power Model on ln(T3)	A3-17
Power Model of T4	A3-18
Power Model of ln(T4)	A3-19

Figures follow for these fits.

*No figure for this fit.

Table A3-1 – USEPA BMDs from Power Function fits to 90 day study, 14 day time point, male and female rats combined. Benchmark response set at 10% less than control.

Endpoint		p of fit	BMD	BMDL	NOAEL/ LOAEL	BMDL: N(L)OAEL	BMD: N(L)OAEI	BMR: 10% CTL SD
TSH	power	0.45	0.037	0.000075	0.01	.0075	3.7	1.26 2.52
	quadratic	0.069	fit signif but not monotonic		0.01			
ln TSH	power	0.43	0.043	could not calc. BMDL	0.01	NA	4.3	-0.1053
	quadratic	fit not signif, non-monotonic			0.01			
T3	power	0.41	0.000033	lower limit incl. 0	0.01*	NA	0.0033	16.65 38.51
	quadratic	fit not signif, non-monotonic			0.01*			
lnT3	power	0.35	0.000168	lower limit incl. 0	0.01*	NA	0.0168	-0.1053
	quadratic	fit not signif, non-monotonic			0.01*			
T4	power	0.203	1.16	0.0035	1.0	0.0035	1.16	0.506 0.603
	quadratic [†]	0.12	3.27	1.09	1.0	1.09	3.27	
ln (T4)	power	0.22	1.64	0.04	1.0	0.04	1.64	-0.1053
	quadratic [†]	0.16	3.25	1.06	1.0	1.06	3.25	

* LOAEL; otherwise, value is NOAEL

† Global minimum of quadratic function is at dose ≈ 9.50 mg/kg/day

Table A3-2 – BMDLs from Subchronic Study, 14 day time point, male and female combined.
BMRs at CTL - 10%, 20%, 40% of CTL.

	p of fit	-10%	-20%	-40%	mean	NOAEL	
T4	0.203	0.0035	1.21	38.33	5.066	1.0	power fcn fit
ln(T4)	0.22	0.037	3.899	36.48		1.0	power fcn fit
T3	0.41	Lower limit includes 0	Lower limit includes 0	0.129*	166.5	0.01**	power fcn fit
ln(T3)	0.35	Lower limit includes 0	.000054*	43.16*		0.01**	powerfcn fit
TSH	0.45	0.000076	0.005	0.36	12.616	0.01	power fcn fit
ln(TSH)	0.43	0.0015	0.098	6.587		0.01	power fcn fit

*BMDL calculation failed at a number of values. This means BMDL value may not be accurate.

**LOAEL not NOAEL.

Table A3-3 – USEPA BMDs from fits to Subchronic study, 90 day time point, male and female rats combined. BMR set at 10% less than control.

Endpoint	p of fit	BMD	BMDL	NOAEL/ LOAEL	BMD: N(L)OAEL	BMDL: N(L)OAEL	BMR: 10% CTL SD
TSH †	0.42	0.269	0.018	0.05	5.38	0.36	1.633 1.464
ln TSH †	0.40	0.492	0.0796	0.05	9.84	1.6	-0.1053
T3 †	0.01	no significant fit		0.01*	NA	NA	17.50 18.924
lnT3 †	0.01	no significant fit		0.01*	NA	NA	NA
T4 †	0.14	6e-6	lower limit incl. 0	0.01*	6e-4	NA	0.475 0.576
ln (T4)†	0.17	1.10e-5	0.00	0.01*	1.1e-3	∞	-0.1053

* LOAEL; otherwise, value is NOAEL

† Unrestricted quadratic: fit non-monotonic, not significant.

Restricted polynomial (linear): fit not significant

Table A3-4 – BMDLs from Subchronic Study, 90 day time point, male and female combined. BMRs at CTL - 10%, 20%, 40% of CTL.

	p of fit	-10%	-20%	-40%	mean	NOAEL	
T4	0.14	Lower limit includes 0	0.000001	0.53*	4.75	0.01**	power fcn fit
ln(T4)	0.165	0.00	0.004	4.87		0.01**	power fcn fit
T3	0.01	no significant fit			174.96	0.01**	power fcn fit
ln(T3)	0.01	no significant fit				0.01**	powerfcn fit
TSH	0.43	0.019	2.404	73.80	16.33	0.05	power fcn fit
ln(TSH)	0.40	0.082	7.94	405.14		0.05	power fcn fit

*BMDL calculation failed at a number of values. This means BMDL value may not be accurate.

**LOAEL not NOAEL.

Subchronic (90 day study): 14 Day Time point

Power Model TSH of 14 day suchronic
male and female combined: BMR = 0.90 CTL
Input Data File: SBCH14D.SET

Thu Nov 12

10:53:51 1998

BMDS MODEL RUN

The form of the response function is:

$Y[\text{dose}] = \text{control} + \text{slope} * \text{dose}^{\text{power}}$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

The sign of the slope is not restricted

Total number of dose groups = 6

Total number of records with missing values = 0

HERE is the pooled variance 9.89438

Default Initial Parameter Values

var_const = 10.4492

control = 12.616

slope = 3.70392

power = 0.339771

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	10.0389	1.33563
control	12.6906	0.532097
slope	3.60256	0.500178
power	0.317741	0.101959

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	control	slope	power
var_const	1	0.0062	-0.0056	0.011
control	0.0062	1	-0.81	0.57
slope	-0.0056	-0.81	1	-0.52
power	0.011	0.57	-0.52	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	20	12.616	2.520	12.691	10.039
0.0100	15	13.179	2.634	13.525	10.039
0.0500	19	14.471	2.584	14.081	10.039
0.2000	19	15.315	3.194	14.851	10.039
1.0000	20	15.695	3.535	16.293	10.039
10.0000	20	20.299	4.347	20.178	10.039

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma^2$

Model A2: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma_i^2$

Model R: $Y_i = \mu + e_i$
 $\text{Var}\{e_i\} = \sigma^2$

Likelihoods of Interest

Model	Log(Likelihood)	DF	AIC
A1	-185.496159	7	-192.496159
A2	-181.174835	12	-193.174835
fitted	-186.815260	4	-190.815260
R	-222.740002	2	-224.740002

Test 1: Does response and/or variances differ among Dose levels

(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	p-value
Test 1	74.4877	<.00001
Test 2	8.64265	0.1242
Test 3	2.6382	0.4508

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

Benchmark Dose Computation

Specified effect = 1.260000

Risk Type = Added response

Confidence level = 0.950000

BMD = 0.036653

BMDL = 0.000075

 Polynomial Model TSH of 14 day, subchronic
 male and female combine: BMR 0.90 CTL
 Input Data File: SBCH14D.SET
 Thu Nov 12 10:59:21 1998

10.0000 20 20.299 4.347 18.496 10.441

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu(i) + e(ij)$
 $\text{Var}\{e(ij)\} = \sigma^2$

Model A2: $Y_{ij} = \mu(i) + e(ij)$
 $\text{Var}\{e(ij)\} = \sigma^2(i)^2$

Model R: $Y_i = \mu + e(i)$
 $\text{Var}\{e(i)\} = \sigma^2$

BMDS MODEL RUN

The form of the response function is:

$$Y[\text{dose}] = \beta_0 + \beta_1 \cdot \text{dose} + \beta_2 \cdot \text{dose}^2 + \dots$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

Signs of the polynomial coefficients are not restricted

Total number of dose groups = 6

Total number of records with missing values = 0

Default Initial Parameter Values

var_const =	10.4492
beta_0 =	13.6643
beta_1 =	2.49852
beta_2 =	-0.183528

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	10.4414	1.38911
beta_0	13.6807	0.409052
beta_1	2.46277	0.955252
beta_2	-0.180117	0.0935933

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	beta_0	beta_1	beta_2
var_const	1	-1.6e-006	4.5e-006	-4.5e-006
beta_0	-1.6e-006	1	-0.57	0.54
beta_1	4.5e-006	-0.57	1	-1
beta_2	-4.5e-006	0.54	-1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	20	12.616	2.520	13.681	10.441
0.0100	15	13.179	2.634	13.704	10.441
0.0500	19	14.471	2.584	13.794	10.441
0.2000	19	15.315	3.194	14.130	10.441
1.0000	20	15.695	3.535	15.783	10.441

Likelihoods of Interest

Model	Log(Likelihood)	DF	AIC
A1	-185.496159	7	-192.496159
A2	-181.174835	12	-193.174835
fitted	-189.036709	4	-193.036709
R	-425.398793	2	-427.398793

Test 1: Does response and/or variances differ among dose levels

(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	p-value
Test 1	479.805	<.00001
Test 2	8.64265	0.1242
Test 3	7.0811	0.06936

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

Benchmark Dose Computation

Specified effect = 1.260000
 Risk Type = Added response
 Confidence level = 0.950000
 BMD = 0.532345
 BMDL = 0.320301

Power Model on ln TSH. Subchronic. 14 day. 0.90 CTL
Input Data File: SBCH14DLN.SET

Tue Nov 10 15:30:07 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[\text{dose}] = \text{control} + \text{slope} * \text{dose}^{\text{power}}$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

The sign of the slope is not restricted

Total number of dose groups = 6

Total number of records with missing values = 0

HERE is the pooled variance 0.0399153

Default Initial Parameter Values

var_const = 0.0421536

control = 2.516

slope = 0.249657

power = 0.305549

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.0405341	0.00539259
control	2.51787	0.0340839
slope	0.247911	0.0343465
power	0.271506	0.0944814

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	control	slope	power
var_const	1	0.001	-0.00091	0.0021
control	0.001	1	-0.82	0.51
slope	-0.00091	-0.82	1	-0.44
power	0.0021	0.51	-0.44	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	20	2.516	0.198	2.518	0.041
0.0100	15	2.560	0.190	2.589	0.041
0.0500	19	2.657	0.178	2.628	0.041
0.2000	19	2.704	0.214	2.678	0.041
1.0000	20	2.729	0.227	2.766	0.041
10.0000	20	2.989	0.216	2.981	0.041

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu(i) + e(ij)$
 $\text{Var}\{e(ij)\} = \sigma^2$

Model A2: $Y_{ij} = \mu(i) + e(ij)$
 $\text{Var}\{e(ij)\} = \sigma^2(i)$

Model R: $Y_i = \mu + e(i)$
 $\text{Var}\{e(i)\} = \sigma^2$

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	125.986223	7	118.986223
A2	126.277167	12	114.277167
fitted	124.617067	4	120.617067
R	91.745222	2	89.745222

Test 1: Does response and/or variances differ among Dose levels

(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test -2*log(Likelihood Ratio) p-value

Test 1	68.482	<.00001
Test 2	0.581888	0.9888
Test 3	2.73831	0.4338

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

Benchmark Dose Computation

Specified effect = 0.105300

Risk Type = Added response

Confidence level = 0.950000

BMD = 0.042692

BMDL = 0.042692

BMDL curve computation failed for BMR = -0.059125 .

The BMDL curve appearing in the graph may not be accurate.

BMDL curve computation failed for BMR = -0.118250 . The BMDL curve appearing in the graph may not be accurate.

BMDL curve computation failed for BMR = -0.177375 . The BMDL curve appearing in the graph may not be accurate.

BMDL curve computation failed for BMR = -0.236500 . The BMDL curve appearing in the graph may not be accurate.

Power Model of T3 14 day of subchronic study
 male and female combined, BMR 0.90 CTL
 Input Data File: SBCH14D.SET
 Thu Nov 12 10:21:30 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[\text{dose}] = \text{control} + \text{slope} * \text{dose}^{\text{power}}$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

The sign of the slope is not restricted

Total number of dose groups = 6

Total number of records with missing values = 0

HERE is the pooled variance 407.506

Default Initial Parameter Values

var_const = 430.357

control = 166.5

slope = -37.667

power = 0.091595

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	414.362	55.1266
control	166.651	4.24469
slope	-37.726	4.9516
power	0.0793406	0.0672036

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	control	slope	power
var_const	1	0.00045	-0.00024	-0.0051
control	0.00045	1	-0.89	-0.089
slope	-0.00024	-0.89	1	0.047
power	-0.0051	-0.089	0.047	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	20	166.500	38.512	166.651	414.362
0.0100	15	143.898	19.973	140.471	414.362

0.0500	19	135.257	13.600	136.906	414.362
0.2000	19	134.840	15.106	133.447	414.362
1.0000	20	124.437	11.509	128.925	414.362
10.0000	20	123.674	11.073	121.363	
			414.362		

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu(i) + e(ij)$
 $\text{Var}\{e(ij)\} = \sigma^2$

Model A2: $Y_{ij} = \mu(i) + e(ij)$
 $\text{Var}\{e(ij)\} = \sigma^2(i)$

Model R: $Y_i = \mu + e(i)$
 $\text{Var}\{e(i)\} = \sigma^2$

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-395.568197	7	-402.568197
A2	-369.482451	12	-381.482451
fitted	-397.010823	4	-401.010823
R	-426.597904	2	-428.597904

Test 1: Does response and/or variances differ among Dose levels

(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	p-value
Test 1	62.0594	<.00001
Test 2	52.1715	<.00001
Test 3	2.88525	0.4097

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

The p-value for Test 2 is less than .05. Variances may not be homogeneous

Benchmark Dose Computation

Specified effect = 16.650000

Risk Type = Added response

Confidence level = 0.950000

BMD = 0.000033

BMDL computation failed. Lower limit includes zero.

Power Model of ln(T3) from subchronic 14 day
time point BMR 0.90 ctl

Input Data File: SBCH14DLN.SET
Tue Nov 10 15:22:02 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[\text{dose}] = \text{control} + \text{slope} * \text{dose}^{\text{power}}$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

The sign of the slope is not restricted

Total number of dose groups = 6

Total number of records with missing values = 0

HERE is the pooled variance 0.0179807

Default Initial Parameter Values

var_const	=	0.0189889
control	=	5.089
slope	=	-0.235518
power	=	0.10919

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.0183437	0.00244047
control	5.09047	0.0276333
slope	-0.236424	0.0323033
power	0.0930608	0.0671755

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	control	slope	power
var_const	1	0.0008	-0.00048	-0.0071
control	0.0008	1	-0.89	-0.11
slope	-0.00048	-0.89	1	0.068
power	-0.0071	-0.11	0.068	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	20	5.089	0.235	5.090	0.018
0.0100	15	4.960	0.137	4.936	0.018
0.0500	19	4.902	0.100	4.912	0.018
0.2000	19	4.898	0.110	4.887	0.018
1.0000	20	4.820	0.095	4.854	0.018
10.0000	20	4.814	0.089	4.798	0.018

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma^2$

Model A2: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma_i^2$

Model R: $Y_i = \mu + e_i$
 $\text{Var}\{e_i\} = \sigma^2$

Likelihoods of Interest

Model	Log(Likelihood)	DF	AIC
A1	171.042896	7	164.042896
A2	186.510819	12	174.510819
fitted	169.413502	4	165.413502
R	141.953188	2	139.953188

Test 1: Does response and/or variances differ among Dose levels

(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	p-value
Test 1	58.1794	<.00001
Test 2	30.9358	<.00001
Test 3	3.25879	0.3534

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

The p-value for Test 2 is less than .05. Variances may not be homogeneous

Benchmark Dose Computation

Specified effect = 0.105300

Risk Type = Added response

Confidence level = 0.950000

BMD = 0.000168

BMDL computation failed. Lower limit includes zero.

P = 0.35; fit is significant

Power Model of T4, 14 day time point of
subchronic study
male and female combined, BMR 0.90 CTL
Input Data File: SBCH14D.SET
Thu Nov 12 10:30:17 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[\text{dose}] = \text{control} + \text{slope} * \text{dose}^{\text{power}}$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

The sign of the slope is not restricted

Total number of dose groups = 6

Total number of records with missing values = 0

HERE is the pooled variance 0.408752

Default Initial Parameter Values

var_const	=	0.431673
control	=	5.066
slope	=	-0.57726
power	=	0.129776

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.422017	0.0576254
control	4.97416	0.160168
slope	-0.484493	0.147626
power	0.29001	0.347332

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	control	slope	power
var_const	1	-0.18	0.17	0.23
control	-0.18	1	-0.9	-0.82
slope	0.17	-0.9	1	0.77
power	0.23	-0.82	0.77	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	20	5.066	0.776	4.974	0.422
0.0100	15	4.633	0.687	4.847	0.422
0.0500	19	4.709	0.601	4.771	0.422
0.2000	19	4.695	0.655	4.670	0.422

1.0000	20	4.648	0.696	4.490	0.422
10.0000	20	3.975	0.498	4.029	0.422

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma^2$

Model A2: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma_i^2$

Model R: $Y_i = \mu + e_i$
 $\text{Var}\{e_i\} = \sigma^2$

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-5.452441	7	-12.452441
A2	-3.808564	12	-15.808564
fitted	-7.756958	4	-11.756958
R	-21.333784	2	-23.333784

Test 1: Does response and/or variances differ among Dose levels

(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	p-value
------	--------------------------	---------

Test 1	31.7627	<.00001
Test 2	3.28776	0.6557
Test 3	4.60903	0.2028

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

Benchmark Dose Computation

Specified effect = 0.506000

Risk Type = Added response

Confidence level = 0.950000

BMD = 1.161563

BMDL = 0.003519

 Polynomial Model of T4 14 day, Subchronic
 male and female combined: BMR 0.90 CTL
 Input Data File: SBCH14D.SET
 Thu Nov 12 10:43:52 1998

10.0000 20 3.975 0.498 4.082 0.427

BMDS MODEL RUN

The form of the response function is:

$$Y[dose] = \beta_0 + \beta_1 * dose + \beta_2 * dose^2 + \dots$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

Signs of the polynomial coefficients are not restricted

Total number of dose groups = 6

Total number of records with missing values = 0

Default Initial Parameter Values

var_const = 0.431673

beta_0 = 4.79167

beta_1 = -0.172195

beta_2 = 0.00905448

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.426878	0.056791
beta_0	4.80593	0.0827085
beta_1	-0.189803	0.193148
beta_2	0.0106728	0.0189242

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	beta_0	beta_1	beta_2
var_const	1	8.9e-011	-2.3e-010	2.7e-010
beta_0	8.9e-011	1	-0.57	0.54
beta_1	-2.3e-010	-0.57	1	-1
beta_2	2.7e-010	0.54	-1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	20	5.066	0.776	4.806	0.427
0.0100	15	4.633	0.687	4.804	0.427
0.0500	19	4.709	0.601	4.797	0.427
0.2000	19	4.695	0.655	4.771	0.427
1.0000	20	4.648	0.696	4.637	0.427

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu_i + \epsilon_{ij}$
 $\text{Var}\{\epsilon_{ij}\} = \sigma^2$

Model A2: $Y_{ij} = \mu_i + \epsilon_{ij}$
 $\text{Var}\{\epsilon_{ij}\} = \sigma_i^2$

Model R: $Y_i = \mu + \epsilon_i$
 $\text{Var}\{\epsilon_i\} = \sigma^2$

Likelihoods of Interest

Model	Log(Likelihood)	DF	AIC
A1	-5.452441	7	-12.452441
A2	-3.808564	12	-15.808564
fitted	-8.403928	4	-12.403928
R	-229.262178	2	-231.262178

Test 1: Does response and/or variances differ among dose levels

(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	p-value
Test 1	447.619	<.00001
Test 2	3.28776	0.6557
Test 3	5.90297	0.1164

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

Benchmark Dose Computation

Specified effect = 0.506000

Risk Type = Added response

Confidence level = 0.950000

BMD = 3.265564

BMDL = 1.090297

 Power Model of ln(T4) from subchroninc. 14
 day. 0.90 BMR
 Input Data File: SBCH14DLN.SET

Tue Nov 10 14:59:09 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[\text{dose}] = \text{control} + \text{slope} * \text{dose}^{\text{power}}$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

The sign of the slope is not restricted

Total number of dose groups = 6

Total number of records with missing values = 0

HERE is the pooled variance 0.0193106

Default Initial Parameter Values

var_const = 0.0203934

control = 1.611

slope = -0.119781

power = 0.140323

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.0199074	0.00272691
control	1.58469	0.0315801
slope	-0.0878567	0.0265585
power	0.365187	0.317794

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	control	slope	power
var_const	1	-0.19	0.18	0.24
control	-0.19	1	-0.89	-0.81
slope	0.18	-0.89	1	0.77
power	0.24	-0.81	0.77	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	20	1.611	0.154	1.585	0.020
0.0100	15	1.523	0.150	1.568	0.020
0.0500	19	1.540	0.131	1.555	0.020

0.2000	19	1.537	0.145	1.536	0.020
1.0000	20	1.526	0.150	1.497	0.020
10.0000	20	1.373	0.126	1.381	0.020

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma^2$

Model A2: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma_i^2$

Model R: $Y_i = \mu + e_i$
 $\text{Var}\{e_i\} = \sigma^2$

Likelihoods of Interest

Model	Log(Likelihood)	DF	AIC
A1	167.011259	7	160.011259
A2	167.136253	12	155.136253
fitted	164.791638	4	160.791638
R	150.686155	2	148.686155

Test 1: Does response and/or variances differ among Dose levels

(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	p-value
Test 1	32.6502	<.00001
Test 2	0.249988	0.9985
Test 3	4.43924	0.2178

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

Benchmark Dose Computation

Specified effect = 0.105300

Risk Type = Added response

Confidence level = 0.950000

BMD = 1.642019

BMDL = 0.037058

p = 0.22; fit is significant

**Polynomial Model of ln(T4) on subchronic 14
day time point BMR 0.90 ctl**
Input Data File: SBCHI14DLN.SET
Tue Nov 10 15:17:37 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[\text{dose}] = \beta_0 + \beta_1 * \text{dose} + \beta_2 * \text{dose}^2 + \dots$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

Signs of the polynomial coefficients are not restricted

Total number of dose groups = 6

Total number of records with missing values = 0

Default Initial Parameter Values

var_const = 0.0203934

beta_0 = 1.55596

beta_1 = -0.0354251

beta_2 = 0.0017132

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.0200435	0.00266654
beta_0	1.5589	0.0179219
beta_1	-0.0390587	0.0418528
beta_2	0.00204727	0.00410063

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	beta_0	beta_1	beta_2
var_const	1	5.1e-008	-8.4e-008	8.5e-008
beta_0	5.1e-008	1	-0.57	0.54
beta_1	-8.4e-008	-0.57	1	-1
beta_2	8.5e-008	0.54	-1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	20	1.611	0.154	1.559	0.020
0.0100	15	1.523	0.150	1.559	0.020
0.0500	19	1.540	0.131	1.557	0.020
0.2000	19	1.537	0.145	1.552	0.020
1.0000	20	1.526	0.150	1.524	0.020
10.0000	20	1.373	0.126	1.394	0.020

Model Descriptions for likelihoods calculatedModel A1: $Y_{ij} = \mu(i) + e(ij)$

$$\text{Var}\{e(ij)\} = \sigma^2$$

Model A2: $Y_{ij} = \mu(i) + e(ij)$

$$\text{Var}\{e(ij)\} = \sigma(i)^2$$

Model R: $Y_i = \mu + e(i)$

$$\text{Var}\{e(i)\} = \sigma^2$$

Likelihoods of Interest

Model	Log(Likelihood)	DF	AIC
A1	167.011259	7	160.011259
A2	167.136253	12	155.136253
fitted	164.406645	4	160.406645
R	-18.028463	2	-20.028463

Test 1: Does response and/or variances differ among dose levels

(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test -2*log(Likelihood Ratio) p-value

Test 1	370.079	<.00001
Test 2	0.249988	0.9985
Test 3	5.20923	0.1571

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

Benchmark Dose Computation

Specified effect = 0.105400

Risk Type = Added response

Confidence level = 0.950000

BMD = 3.253247

BMDL = 1.064168

p = 0.16; fit is significant

Subchronic (90 day study): 90 Day Time point

Power Model of TSH from subchronic, 90 day time point

male and female combined: BMR = 0.90 CTL

Input Data File: DAY90LIN.SET

Thu Nov 12

14:18:02 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[\text{dose}] = \text{control} + \text{slope} * \text{dose}^{\text{power}}$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

The sign of the slope is not restricted

Total number of dose groups = 6

Total number of records with missing values = 0

HERE is the pooled variance 2.73237

Default Initial Parameter Values

var_const	=	2.87746
control	=	16.333
slope	=	2.04505
power	=	0.263006

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	2.77383	0.35972
control	16.2602	0.283087
slope	2.1171	0.319071
power	0.199257	0.0764695

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	control	slope	power
var_const	1	-0.0088	0.0068	-0.026
control	-0.0088	1	-0.83	0.35
slope	0.0068	-0.83	1	-0.27
power	-0.026	0.35	-0.27	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
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0.0000	20	16.333	1.464	16.260	2.774
0.0100	20	16.812	1.740	17.106	2.774

0.0500	20	17.340	1.690	17.426	2.774
0.2000	20	18.175	1.795	17.796	2.774
1.0000	19	18.371	1.603	18.377	2.774
10.0000	20	19.544	1.852	19.610	2.774

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma^2$

Model A2: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma_i^2$

Model R: $Y_i = \mu + e_i$
 $\text{Var}\{e_i\} = \sigma^2$

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-118.807670	7	-125.807670
A2	-118.608502	12	-130.608502
fitted	-120.203728	4	-124.203728
R	-144.271045	2	-146.271045

Test 1: Does response and/or variances differ among Dose levels

(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	p-value
Test 1	50.9267	<.00001
Test 2	0.398337	0.9954
Test 3	2.79212	0.4248

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

Benchmark Dose Computation

Specified effect = 1.630000

Risk Type = Added response

Confidence level = 0.950000

BMD = 0.269222

BMDL = 0.018309

p = 0.42: fit is significant

Power Model ln(TSH) subchronic, 90 day time point
 male and female combine, BMR 0.90 CTL
 Input Data File: DAY90THYROID.SET
 Thu Nov 12 13:14:53 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[\text{dose}] = \text{control} + \text{slope} * \text{dose}^{\text{power}}$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

The sign of the slope is not restricted

Total number of dose groups = 6

Total number of records with missing values = 0

HERE is the pooled variance 0.00861677

Default Initial Parameter Values

var_const = 0.0090743

control = 2.7894

slope = 0.116661

power = 0.256888

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.0087591	0.00113592
control	2.78517	0.0160313
slope	0.120654	0.0182084
power	0.191801	0.0746563

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	control	slope	power
var_const	1	-0.0085	0.0065	-0.026
control	-0.0085	1	-0.84	0.33
slope	0.0065	-0.84	1	-0.25
power	-0.026	0.33	-0.25	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	20	2.789	0.090	2.785	0.009
0.0100	20	2.817	0.101	2.835	0.009
0.0500	20	2.849	0.097	2.853	0.009

0.2000	20	2.895	0.099	2.874	0.009
1.0000	19	2.907	0.089	2.906	0.009
10.0000	20	2.968	0.096	2.973	0.009

Model Descriptions for likelihoods calculated

$$\text{Model A1: } Y_{ij} = \mu(i) + e(ij)$$

$$\text{Var}\{e(ij)\} = \sigma^2$$

$$\text{Model A2: } Y_{ij} = \mu(i) + e(ij)$$

$$\text{Var}\{e(ij)\} = \sigma(i)^2$$

$$\text{Model R: } Y_i = \mu + e(i)$$

$$\text{Var}\{e(i)\} = \sigma^2$$

Warning: Likelihood for model A1 larger than or equal to that one for model A2.

Likelihoods of Interest

Model	Log(Likelihood)	DF	AIC
A1	223.865645	7	216.865645
A2	223.599715	12	211.599715
fitted	222.390906	4	218.390906
R	198.585575	2	196.585575

Test 1: Does response and/or variances differ among Dose levels

(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test -2*log(Likelihood Ratio) p-value

Test	-2*log(Likelihood Ratio)	p-value
Test 1	50.5601	<.00001
Test 2	0	<.00001
Test 3	2.94948	0.3995

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

The p-value for Test 2 is less than .05. Variances may not be homogeneous

Benchmark Dose Computation

Specified effect = 0.105300

Risk Type = Added response

Confidence level = 0.950000

BMD = 0.491819

BMDL = 0.079570

p = 0.40; fit is significant

Power Model of T3 Subchron 90 day time point
 male and female combined; BMR 0.90 CTL
 Input Data File: DAY90LIN.SET
 Thu Nov 12 13:44:06 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[\text{dose}] = \text{control} + \text{slope} * \text{dose}^{\text{power}}$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

The sign of the slope is not restricted

Total number of dose groups = 6

Total number of records with missing values = 0

HERE is the pooled variance 225.647

Default Initial Parameter Values

var_const = 237.628

control = 174.958

slope = -48.9702

power = 0.107995

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	244.943	31.7584
control	175.381	3.192
slope	-48.8447	3.76744
power	0.0869396	0.0335076

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	control	slope	power
var_const	1	0.0015	-0.00083	-0.016
control	0.0015	1	-0.89	-0.099
slope	-0.00083	-0.89	1	0.053
power	-0.016	-0.099	0.053	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	20	174.958	18.924	175.381	244.943
0.0100	20	150.298	17.009	142.652	244.943
0.0500	20	133.969	16.994	137.736	244.943
0.2000	20	129.861	15.093	132.914	244.943
1.0000	19	122.137	10.432	126.536	244.943
10.0000	20	119.488	12.089	115.711	244.943

Model Descriptions for likelihoods calculated

$$\text{Model A1: } Y_{ij} = \mu_i + e_{ij}$$

$$\text{Var}\{e_{ij}\} = \sigma^2$$

$$\text{Model A2: } Y_{ij} = \mu_i + e_{ij}$$

$$\text{Var}\{e_{ij}\} = \sigma_i^2$$

$$\text{Model R: } Y_i = \mu + e_i$$

$$\text{Var}\{e_i\} = \sigma^2$$

Likelihoods of Interest

Model	Log(Likelihood)	DF	AIC
A1	-381.428764	7	-388.428764
A2	-377.245597	12	-389.245597
fitted	-386.811020	4	-390.811020
R	-478.509375	2	-480.509375

Test 1: Does response and/or variances differ among Dose levels

(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

$$\text{Test} \quad -2\log(\text{Likelihood Ratio}) \quad \text{p-value}$$

Test 1	194.161	<.00001
Test 2	8.36633	0.1372
Test 3	10.7645	0.01307

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

The p-value for Test 3 is less than .05. You may want to try a different model

Benchmark Dose Computation

Specified effect = 17.500000

Risk Type = Added response

Confidence level = 0.950000

BMD = 0.000007

BMDL computation failed. Lower limit includes zero.

p = 0.01; fit is not significant

Power Model on Int3, Subchronic, 90 day time
 point male and female combined, BMR 0.90 CTL
 Input Data File: DAY90THYROID.SET
 Thu Nov 12 13:04:38 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[\text{dose}] = \text{control} + \text{slope} * \text{dose}^{\text{power}}$$

Dependent variable - MEAN

Independent variable - dose

var_power is set to 0

The sign of the slope is not restricted

Total number of dose groups - 6

Total number of records with missing values - 0

HERE is the pooled variance 0.0112321

Default Initial Parameter Values

var_const = 0.0118285

control = 5.1592

slope = -0.329416

power = 0.121853

0.2000	20	4.860	0.117	4.881	0.012
1.0000	19	4.802	0.086	4.834	0.012
10.0000	20	4.779	0.100	4.752	0.012

Model Descriptions for likelihoods calculated

$$\text{Model A1: } Y_{ij} = \mu(i) + e(ij)$$

$$\text{Var}\{e(ij)\} = \sigma^2$$

$$\text{Model A2: } Y_{ij} = \mu(i) + e(ij)$$

$$\text{Var}\{e(ij)\} = \sigma^2(i)^2$$

$$\text{Model R: } Y_i = \mu + e(i)$$

$$\text{Var}\{e(i)\} = \sigma^2$$

Likelihoods of Interest

Model	Log(Likelihood)	DF	AIC
A1	208.094128	7	201.094128
A2	209.359249	12	197.359249
fitted	202.601629	4	198.601629
R	116.341115	2	114.341115

Test 1: Does response and/or variances differ among Dose levels

(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test -2*log(Likelihood Ratio) p-value

Test 1	183.506	<.00001
Test 2	2.53024	0.7719
Test 3	10.985	0.01181

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

The p-value for Test 3 is less than .05. You may want to try a different model

Benchmark Dose Computation

Specified effect = 0.105300

Risk Type = Added response

Confidence level = 0.950000

BMD = 0.000007

BMDL = 0.000000

p = 0.01; fit is not significant

BMDL curve computation failed for BMR = -0.047588.

The BMDL curve appearing in the graph may not be accurate.

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.0122153	0.00158387
control	5.16287	0.0221661
slope	-0.329042	0.0262164
power	0.0961585	0.0341346

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	control	slope	power
var_const	1	0.0022	-0.0013	-0.019
control	0.0022	1	-0.89	-0.12
slope	-0.0013	-0.89	1	0.067
power	-0.019	-0.12	0.067	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	20	5.159	0.106	5.163	0.012
0.0100	20	5.007	0.112	4.952	0.012
0.0500	20	4.890	0.127	4.916	0.012

Power Model of T4, subchronic, 90 day time
 point male and female combined. BMR 0.90 CTL
 Input Data File: DAY90LIN.SET
 Thu Nov 12 13:23:45 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[dose] = control + slope * dose^{power}$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

The sign of the slope is not restricted

Total number of dose groups = 6

Total number of records with missing values = 0

HERE is the pooled variance 0.180002

Default Initial Parameter Values

var_const = 0.18956

control = 4.751

slope = -1.47131

power = 0.103081

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.186903	0.024231
control	4.7559	0.0872289
slope	-1.47062	0.102936
power	0.0944677	0.0362523

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	control	slope	power
var_const	1	0.0011	-0.00062	-0.008
control	0.0011	1	-0.89	-0.14
slope	-0.00062	-0.89	1	0.078
power	-0.008	-0.14	0.078	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	20	4.751	0.576	4.756	0.187
0.0100	20	3.939	0.583	3.804	0.187
0.0500	20	3.514	0.375	3.648	0.187
0.2000	20	3.441	0.341	3.493	0.187
1.0000	19	3.333	0.354	3.285	0.187

10.0000 20 2.938 0.283 2.928 0.187

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma^2$

Model A2: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma^2_{(i)}$

Model R: $Y_i = \mu_i + e_i$
 $\text{Var}\{e_i\} = \sigma^2$

Likelihoods of Interest

Model	Log(Likelihood)	DF	AIC
A1	43.029873	7	36.029873
A2	51.513535	12	39.513535
fitted	40.291269	4	36.291269
R	-66.365471	2	-68.365471

Test 1: Does response and/or variances differ among Dose levels

(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	p-value
Test 1	218.791	<.00001
Test 2	16.9673	0.004562
Test 3	5.47721	0.14

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

The p-value for Test 2 is less than .05. Variances may not be homogeneous

Benchmark Dose Computation

Specified effect = 0.475000

Risk Type = Added response

Confidence level = 0.950000

BMD = 0.000006

BMDL computation failed. Lower limit includes zero.

p = 0.14; fit is significant

Power Model of lnT4. Subchron. 90 day time
 combined male and female. BMR 0.90 CTL
 Input Data File: DAY90THYROID.SET
 Thu Nov 12 12:54:10 1998

10.0000 20 1.073 0.095 1.074 0.013

BMDS MODEL RUN

The form of the response function is:

$$Y[\text{dose}] = \text{control} + \text{slope} * \text{dose}^{\text{power}}$$

Dependent variable - MEAN

Independent variable - dose

var_power is set to 0

The sign of the slope is not restricted

Total number of dose groups - 6

Total number of records with missing values - 0

HERE is the pooled variance 0.012234

Default Initial Parameter Values

var_const - 0.0128836

control - 1.5515

slope - -0.371038

power - 0.118406

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.012662	0.00164156
control	1.55268	0.0221036
slope	-0.37121	0.0260842
power	0.110205	0.0369673

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	control	slope	power
var_const	1	0.0013	-0.00084	-0.0076
control	0.0013	1	-0.88	-0.18
slope	-0.00084	-0.88	1	0.11
power	-0.0076	-0.18	0.11	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	20	1.552	0.118	1.553	0.013
0.0100	20	1.360	0.149	1.329	0.013
0.0500	20	1.251	0.106	1.286	0.013
0.2000	20	1.231	0.097	1.242	0.013
1.0000	19	1.198	0.107	1.181	0.013

Model Descriptions for likelihoods calculated

$$\text{Model A1: } Y_{ij} = \mu(i) + e(ij)$$

$$\text{Var}\{e(ij)\} = \sigma^2$$

$$\text{Model A2: } Y_{ij} = \mu(i) + e(ij)$$

$$\text{Var}\{e(ij)\} = \sigma^2(i)$$

$$\text{Model R: } Y_i = \mu + e(i)$$

$$\text{Var}\{e(i)\} = \sigma^2$$

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	203.010254	7	196.010254
A2	205.533196	12	193.533196
fitted	200.464286	4	196.464286
R	94.321513	2	92.321513

Test 1: Does response and/or variances differ among Dose levels

(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test -2*log(Likelihood Ratio) p-value

Test	-2*log(Likelihood Ratio)	p-value
Test 1	217.377	<.00001
Test 2	5.04588	0.4103
Test 3	5.09194	0.1652

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

Benchmark Dose Computation

Specified effect - 0.105300

Risk Type - Added response

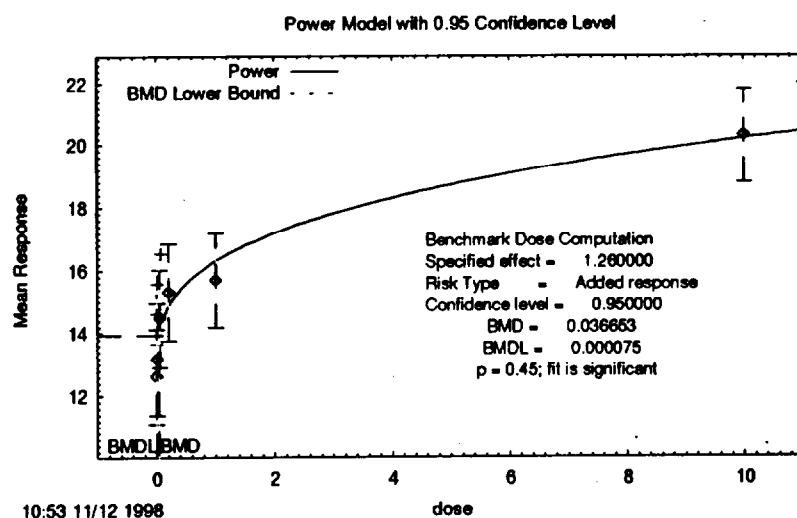
Confidence level - 0.950000

BMD - 0.000011

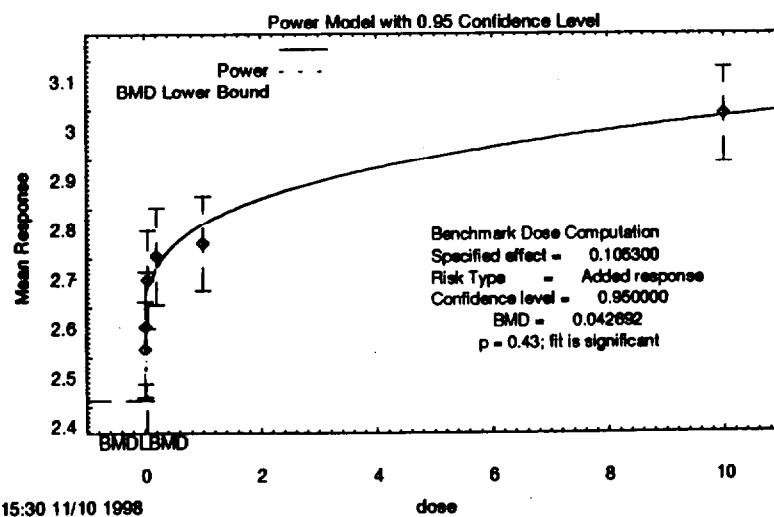
BMDL - 0.000000

p = 0.17; fit is significant

Subchronic Study, 14 Day Time Point TSH, Male and Female Combined

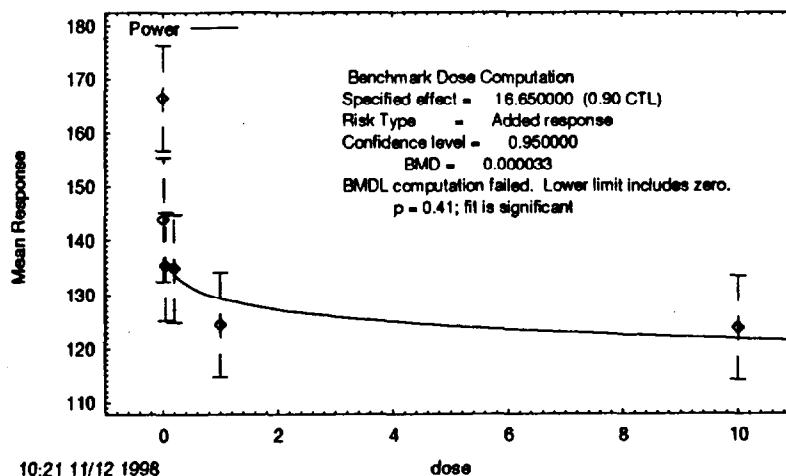


Subchronic Study, 14 Day Time Point In(TSH), Male and Female Combined



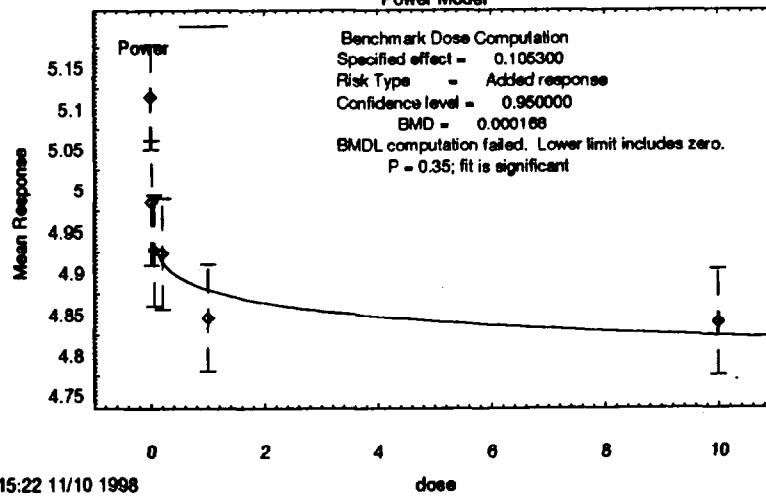
Subchronic Study, 14 Day Time Point T3, Male and Female Combined

Power Model

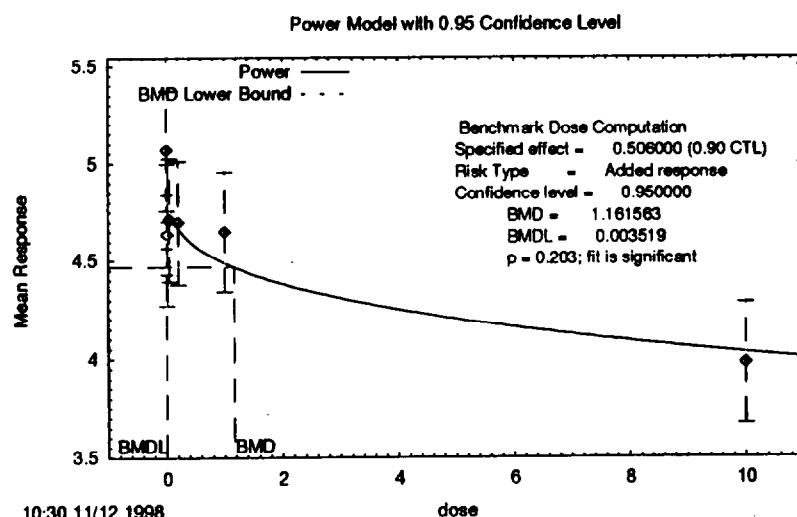


Subchronic Study, 14 Day Time Point ln(T3), Male and Female Combined

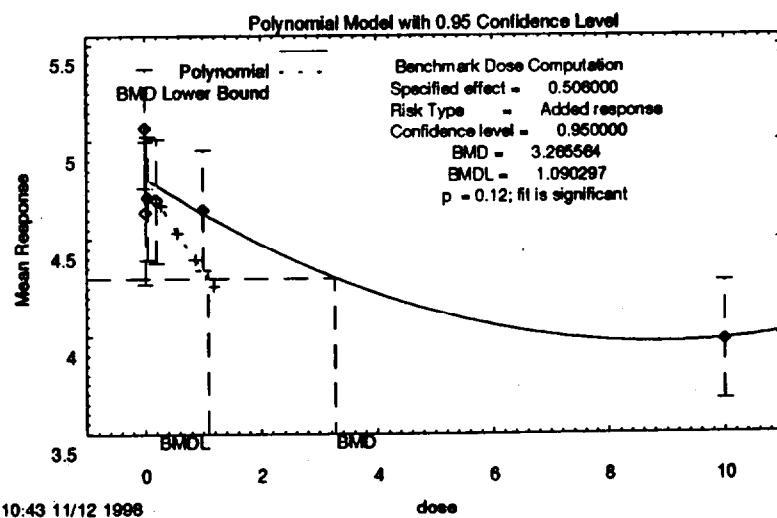
Power Model



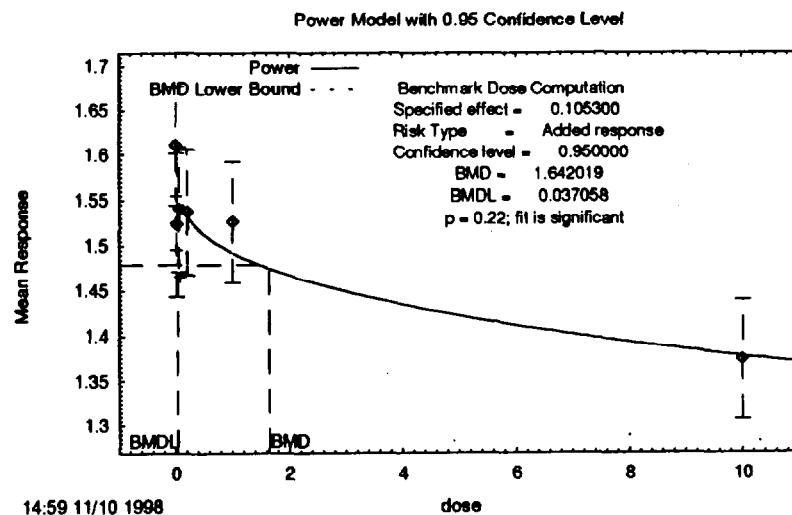
Subchronic Study, 14 Day Time Point T4, Male and Female Combined



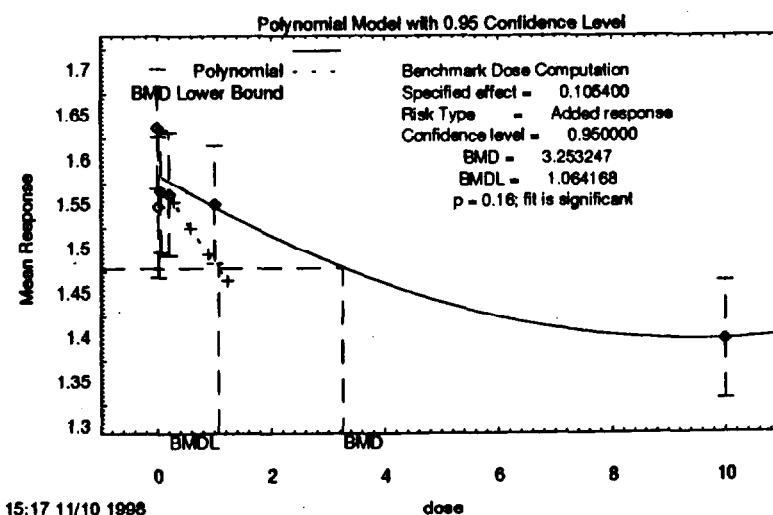
Subchronic Study, 14 Day Time Point T4, Male and Female Combined



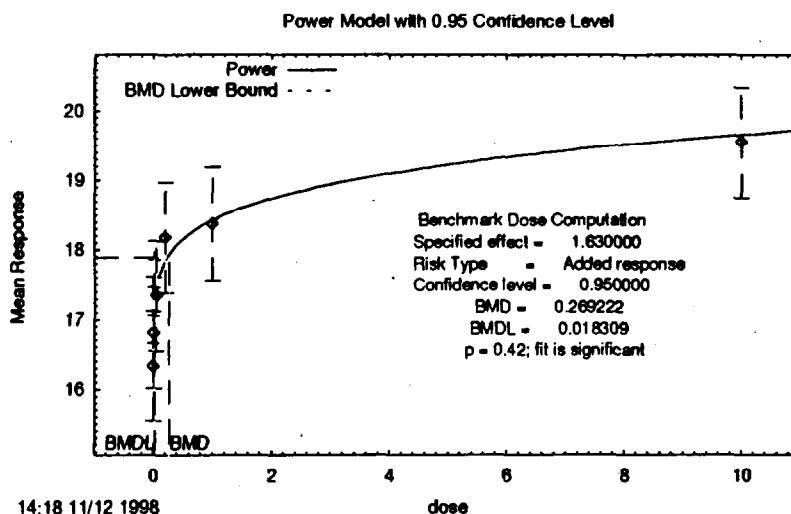
Subchronic Study, 14 Day Time Point In(T4), Male and Female Combined



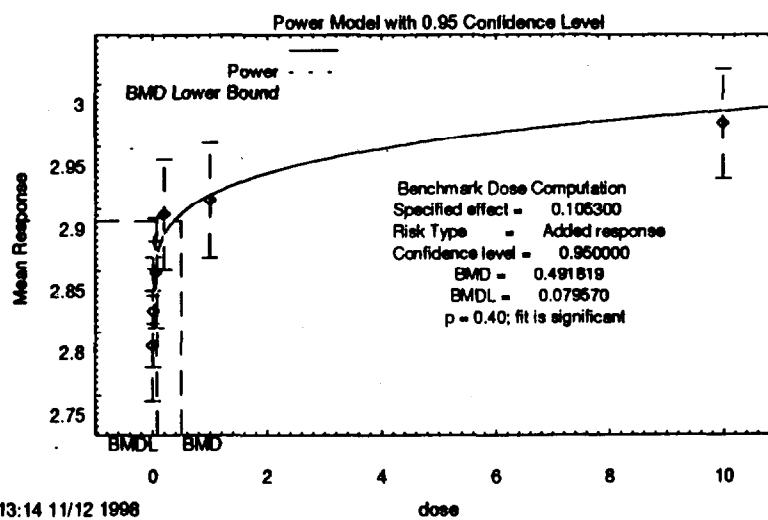
Subchronic Study, 14 Day Time Point In(T4), Male and Female Combined



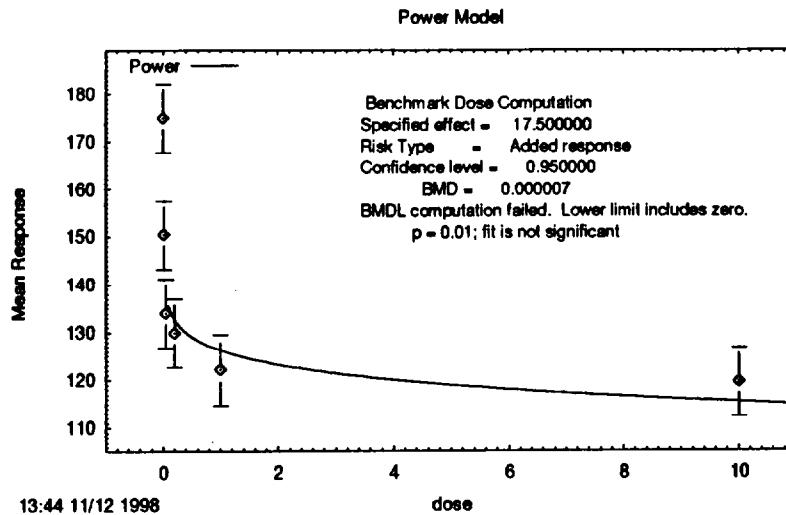
Subchronic Study, 90 Day Time Point TSH, Male and Female Combined



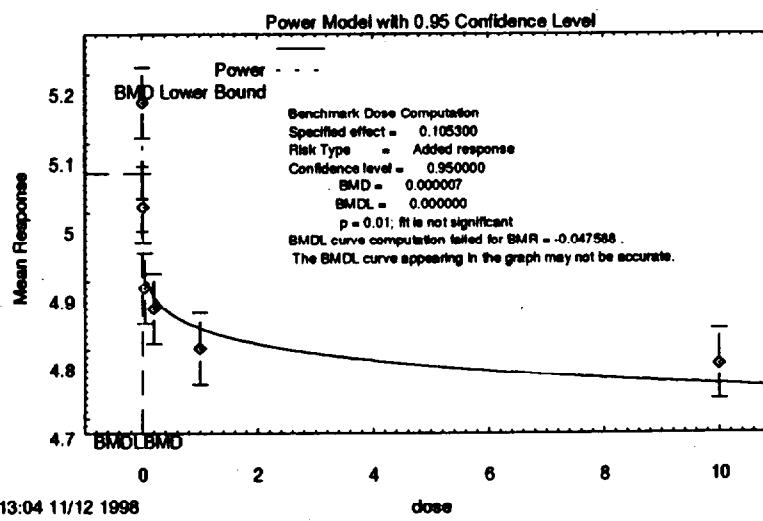
Subchronic Study, 90 Day Time Point In(TSH), Male and Female Combined



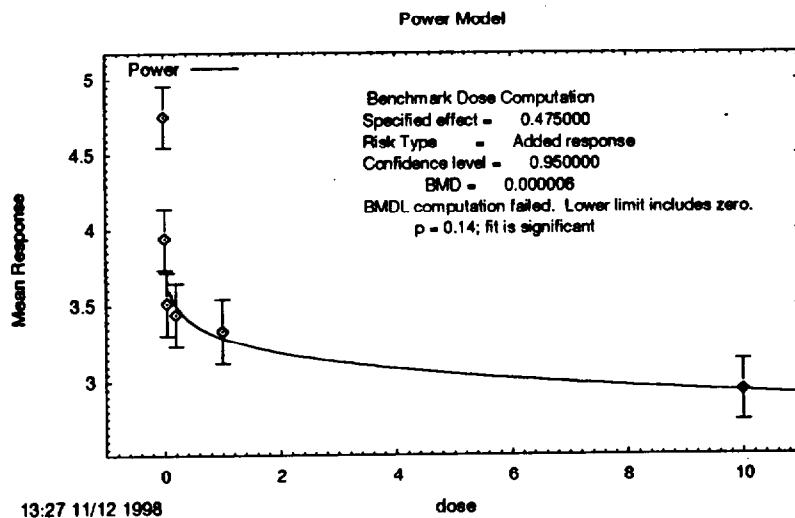
Subchronic Study, 90 Day Time Point T3, Male and Female Combined



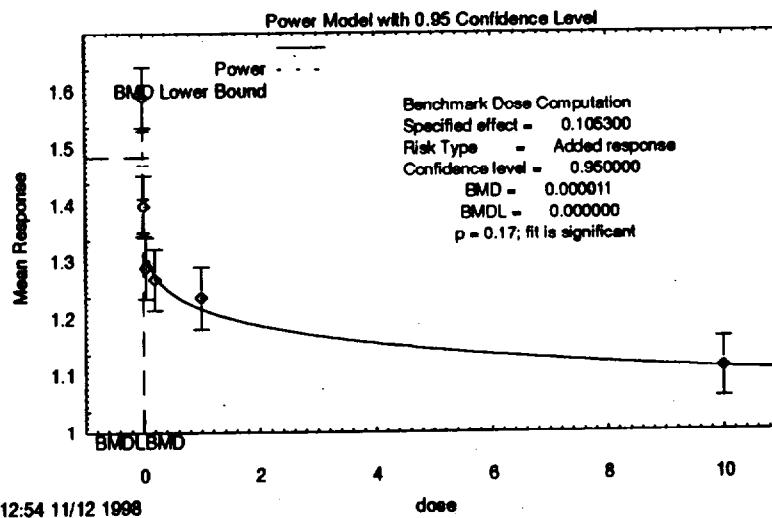
Subchronic Study, 90 Day Time Point ln(T3), Male and Female Combined



Subchronic Study, 90 Day Time Point T4, Male and Female Combined



Subchronic Study, 90 Day Time Point In(T4), Male and Female Combined



Appendix A4 – BMDs for Developmental Neurotoxicity Study

Table A4-1 – USEPA BMDs from fits to Developmental Neurotox Study, PND5 pups.....A4-2

Table A4-2 – BMDLs from Developmental Neurotoxicology Study, PND5 time point.

BMRs at CTL - 10%, 20%, 40% of CTL.....A4-3

Table A4-3 – BMDs from F1: PND14 Motor Activity Data.....A4-4

Table A4-5 – BMDs from F1: PND5 Subjective Histopathology, Incidence Data.....A4-4

BMDs	A4-5
Linear Model of TSH*	A4-5
Power Model of TSH*	A4-6
Linear Model of ln(TSH)	A4-7
Power Model to lnTSH	A4-8
Polynomial Model to T3	A4-9
Power Model to T3	A4-10
Power Model to LN(T3)	A4-11
Polynomial Model to ln(t3)	A4-12
Linear Model to T4	A4-13
Polynomial Model of T4*	A4-14
Power Model to T4	A4-15
Power Model to ln(T4)	A4-16
Polynomial Model to ln(T4)	A4-17
Linear Model to ln(t4)	A4-18
Morphometry	A4-19
Polynomial Model to morphometry*	A4-19
Power Model of morphometry	A4-20
Power Model of ln morphometry	A4-21
Polynomial Model to Ln morphometry	A4-22
PND14 Motor activity	A4-23
Linear Model to Movement Data*	A4-23
Polynomial Model to Movement Data*	A4-24
Linear Model Dev to Time Data*	A4-25
Polynomial Model to Time Data*	A4-26
Subjective Histopathology, PND5	A4-27
Gamma Model*	A4-27
Logistic Model*	A4-28
Probit Model*	A4-29
Quantal Linear Model*	A4-30
Quantal Quadratic Model*	A4-31
Weibull Model*	A4-32

*Figures follow for these fits.

Table A4-1 – USEPA BMDs from fits to Developmental Neurotox Study, PND5 pups, male and female rats combined. *Italics denote BMDs derived from non-monotonic fits to data.*

Endpoint	p of fit	BMD	BMDL	NOAEL or LOAEL	BMD: N(L)OAEL	BMDL: N(L)OAEL	BMR: 10% CTL SD
TSH	linear	0.50	4.64	3.77	3.0	1.55	1.26
	power	0.31	4.48	1.43	3.0	1.49	0.48
ln TSH	linear	0.48	5.51	4.43	3.0	1.84	0.54
	power	0.30	5.03	2.11	3.0	1.68	0.70
T3	<0.00001 for all	no fit	no fit	0.1	NA	NA	neither linear, quadratic or power fcns fit data
ln T3	<0.00001 for all	no fit	no fit	0.1	NA	NA	neither linear, quadratic or power fcns fit data
T4	0.50 min = 7.45 mg/kg	1.26	0.98	1.0	1.26	0.98	0.341 0.370 Non-monotonic quadratic sig fit
ln (T4)	0.50 min = 7.14 mg/kg	1.18	0.92	1.0	1.18	0.92	Non-monotonic quadratic sig fit
Morphometry	0.19 global min = 6.81 mg/kg	<i>1.053</i>	<i>0.644</i>	<i>1.00</i>	<i>1.053</i>	<i>0.644</i>	ctl-10%ctl (=31.78); sd = 0.37 Non-monotonic quadratic sig fit Power fcn BMDL interval incl. 0.00
ln (morph)	0.19 global min = 7.01 mg/kg	0.822	<i>0.538</i>	<i>1.00</i>	0.822	<i>0.538</i>	ctl-10%ctl (= 0.341); sd = 0.37 Non-monotonic quadratic sig fit Power fcn BMDL computational failures

* LOAEL; otherwise, value is NOAEL

Table A4-2 – BMDLs from Developmental Neurotoxicology Study, PND5 time point.
 BMRs at CTL - 10%, 20%, 40% of CTL. Underlined values from non-monotonic quadratic fits.

	p of fit	-10%	-20%	-40%	mean	NOAEL	
T4	<u>0.50</u>	<u>0.973</u>	<u>2.16</u>	<u>Benchmark dose at least 100 times the range of input data.</u>	3.41	1.0	Quadratic fit
ln(T4)	<u>0.50</u>	<u>0.92</u>	<u>NC</u>	<u>NC</u>		1.0	Quadratic fit
T3	<0.00001	NC	NC	NC	87.97	0.1	No fit
ln(T3)	<0.00001		NC	NC		0.1	No fit
TSH	0.50	<u>3.77</u>	NC	NC	4.51	3.0	Linear fit
ln(TSH)	0.48	NC	NC	NC		3.0	Linear fit
Morphometry	<u>0.19</u>	<u>0.64</u>	<u>1.37</u>	<u>Benchmark dose at least 100 times the range of input data.</u>	317.83		
ln(Morphometry)	<u>0.19</u>	<u>0.538</u>	<u>1.204</u>	<u>Benchmark dose at least 100 times the range of input data.</u>			

*BMDL calculation failed at a number of values. This means BMDL value may not be accurate.

**LOAEL not NOAEL.

NC – Not computed

Table A4-3 – BMDs from F1: PND14 Motor Activity Data. Linear fits to data.

Endpoint	p of fit	BMD	BMDL	NOAEL/ LOAEL	BMD: N(L)OAEL	BMDL: N(L)OAEL	BMR: 10% CTL SD
Movement	0.72	1.94	1.04	None	NA	NA	24.45 162.75
Time	0.69	1.33	0.66	None	NA	NA	18.60 184.78

Table A4-4 – BMDLs from BMR = CTL - 10, 20 or 40% of CTL for Motor Activity Data

	p of fit	+ 10% of Ctl	+ 20% of Ctl	+ 40% of Ctl	Ctl mean (std dev)	estimated mean
Movement	0.72	1.04	2.08	4.17	244.5 (162.75)	273.04
Time	0.69	0.66	1.33	2.67	186.05 (184.78)	239.07

**BMDs Computations from Developmental
Neurotoxicity, PND5**

Linear Model of TSH Dev NT, PND5, TSH
BMR = 0.90 CTL
Input Data File: PNDSTSH.SET
Fri Nov 13 09:03:21 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[dose] = \beta_0 + \beta_1 * dose + \beta_2 * dose^2 + \dots$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

Signs of the polynomial coefficients are not restricted

Total number of dose groups = 5

Total number of records with missing values = 0

Default Initial Parameter Values

var_const = 0.245033

beta_0 = 4.54229

beta_1 = 0.0972717

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.234401	0.0359555
beta_0	4.54582	0.066972
beta_1	0.0969544	0.0135674

**Asymptotic Correlation Matrix of Parameter
Estimates**

	var_const	beta_0	beta_1
var_const	1	-8.1e-010	4.7e-010
beta_0	-8.1e-010	1	-0.62
beta_1	4.7e-010	-0.62	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	17	4.512	0.465	4.546	0.234
0.1000	14	4.522	0.436	4.556	0.234
1.0000	18	4.753	0.482	4.643	0.234
3.0000	17	4.774	0.476	4.837	0.234
10.0000	19	5.522	0.582	5.515	0.234

Model Descriptions for likelihoods

calculated

Model A1: $Y_{ij} = \mu(i) + e(ij)$
 $\text{Var}\{e(ij)\} = \sigma^2$

Model A2: $Y_{ij} = \mu(i) + e(ij)$
 $\text{Var}\{e(ij)\} = \sigma^2(i)^2$

Model R: $Y_i = \mu + e(i)$
 $\text{Var}\{e(i)\} = \sigma^2$

Likelihoods of Interest

Model	Log(Likelihood)	DF	AIC
A1	20.347026	6	14.347026
A2	20.756974	10	10.756974
fitted	19.155648	3	16.155648
R	-145.709953	2	-147.709953

Test 1: Does response and/or variances differ among dose levels
(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test -2*log(Likelihood Ratio) p-value

Test 1	332.114	<.00001
Test 2	0.819897	0.9358
Test 3	2.38276	0.4969

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

Benchmark Dose Computation

Specified effect = 0.450000

Risk Type = Added response

Confidence level = 0.950000

BMD = 4.641358

BMDL = 3.766344

p = 0.50; fit is significant

Power Model of TSH
 Input Data File: PND5TSH.SET
 Thu Nov 12 15:12:53 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[\text{dose}] = \text{control} + \text{slope} * \text{dose}^{\text{power}}$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

The sign of the slope is not restricted

Total number of dose groups = 5

Total number of records with missing values = 0

HERE is the pooled variance 0.230619

Default Initial Parameter Values

var_const = 0.245033

control = 4.512

slope = 0.121711

power = 0.971065

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.234378	0.0359519
control	4.53965	0.0683035
slope	0.106562	0.0159736
power	0.960498	0.162336

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	control	slope	power
var_const	1	-2.5e-005	5.9e-005	
control	-2.5e-005	1	-0.63	0.15
slope	5.9e-005	-0.63	1	-0.36
power	-0.00017	0.15	-0.36	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	17	4.512	0.465	4.540	0.234
0.1000	14	4.522	0.436	4.551	0.234

1.0000	18	4.753	0.482	4.646	0.234
3.0000	17	4.774	0.476	4.846	0.234
10.0000	19	5.522	0.582	5.513	0.234

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma^2$

Model A2: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma^2(i)$

Model R: $Y_i = \mu + e_i$
 $\text{Var}\{e_i\} = \sigma^2$

Likelihoods of Interest

Model	Log(Likelihood)	DF	AIC
A1	20.347026	6	14.347026
A2	20.756974	10	10.756974
fitted	19.159889	4	15.159889
R	-6.802192	2	-8.802192

Test 1: Does response and/or variances differ among Dose levels

(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	p-value
Test 1	54.2984	<.00001
Test 2	0.819897	0.9358
Test 3	2.37427	0.3051

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

Benchmark Dose Computation

Specified effect = 0.450000

Risk Type = Added response

Confidence level = 0.950000

BMD = 4.480632

BMDL = 1.431002

p = 0.31; fit is significant

Linear Model of ln(TSH) data from dev nt study; good fit.

Input Data File: PND5TSH.SET
Mon Oct 19 13:41:31 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[dose] = \beta_0 + \beta_1 * dose + \beta_2 * dose^2 + ...$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

Signs of the polynomial coefficients are not restricted

Total number of dose groups = 5

Total number of records with missing values = 0

Default Initial Parameter Values
var_const = 0.0104307
beta_0 = 1.51019
beta_1 = 0.0192242

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.009986	0.00153178
beta_0	1.511	0.0138232
beta_1	0.0191409	0.00280036

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	beta_0	beta_1
var_const	1	1.3e-007	1.6e-007
beta_0	1.3e-007	1	-0.62
beta_1	1.6e-007	-0.62	1

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu(i) + e(ij)$
 $\text{Var}\{e(ij)\} = \sigma^2$

Model A2: $Y_{ij} = \mu(i) + e(ij)$
 $\text{Var}\{e(ij)\} = \sigma^2(i)$

Model R: $Y_i = \mu + e(i)$

$$\text{Var}\{e(i)\} = \sigma^2$$

Warning: Likelihood for model A1 larger than or equal to that one for model A2.

Likelihoods of Interest

Model	Log(likelihood)	DF
A1	154.504099	6
A2	154.148206	10
fitted	153.279254	3
R	-12.149376	2

Test 1: Does response and/or variances differ among dose levels

(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test -2*log(Likelihood Ratio) p-value

Test 1	333.307	<.00001
Test 2	0	<.00001
Test 3	2.44969	0.4845

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

The p-value for Test 2 is less than .05. Variances may not be homogeneous

Benchmark Dose Computation

Specified effect = 0.105400 90% of ctl
Risk Type = Added response
Confidence level = 0.950000
BMD = 5.506531
BMDL = 4.431144

Power Model to InTSH dev nt PND5 data
 Input Data File: PND5TSH.SET
 Thu Nov 12 15:22:40 1998

BMDS MODEL RUN .

The form of the response function is:

$$Y[\text{dose}] = \text{control} + \text{slope} * \text{dose}^{\text{power}}$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

The sign of the slope is not restricted

Total number of dose groups = 5

Total number of records with missing values = 0

HERE is the pooled variance 0.00981714

Default Initial Parameter Values

var_const = 0.0104307

control = 1.502

slope = 0.0285681

power = 0.88234

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.00997771	0.00153051
control	1.50723	0.0143698
slope	0.0250854	0.00395863
power	0.887334	0.161971

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	control	slope	power
var_const	1	0.00018	-0.0004	0.0011
control	0.00018	1	-0.65	0.17
slope	-0.0004	-0.65	1	-0.38
power	0.0011	0.17	-0.38	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	17	1.502	0.098	1.507	0.010
0.1000	14	1.505	0.097	1.510	0.010
1.0000	18	1.554	0.101	1.532	0.010
3.0000	17	1.558	0.104	1.574	0.010
10.0000	19	1.703	0.108	1.701	0.010

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu_i + \epsilon_{ij}$

$$\text{Var}\{\epsilon_{ij}\} = \sigma^2$$

Model A2: $Y_{ij} = \mu_i + \epsilon_{ij}$

$$\text{Var}\{\epsilon_{ij}\} = \sigma_i^2$$

Model R: $Y_i = \mu_i + \epsilon_i$

$$\text{Var}\{\epsilon_i\} = \sigma^2$$

Warning: Likelihood for model A1 larger than or equal to that one for model A2.

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	154.504099	6	148.504099
A2	154.148206	10	144.148206
fitted	153.314599	4	149.314599
R	129.511533	2	127.511533

Test 1: Does response and/or variances differ among Dose levels

(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test -2*log(Likelihood Ratio) p-value

Test 1	49.9851	<.00001
Test 2	0	<.00001
Test 3	2.379	0.3044

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

The p-value for Test 2 is less than .05. Variances may not be homogeneous

Benchmark Dose Computation

Specified effect = 0.105300

Risk Type = Added response

Confidence level = 0.950000

BMD = 5.036285

BMDL = 2.114846

Polynomial Model to T3 PND5 T3 data --
non-monotonic, not signif.

Input Data File: PNNT3.SET
Thu Oct 15 09:20:44 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[dose] = \beta_0 + \beta_1 * dose + \beta_2 * dose^2 + \dots$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

Signs of the polynomial coefficients are not restricted

Total number of dose groups = 5

Total number of records with missing values = 0

Default Initial Parameter Values

var_const =	32.0509
beta_0 =	90.0832
beta_1 =	-20.4167
beta_2 =	1.52322

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	46.3938	8.92849
beta_0	90.15	1.449
beta_1	-20.6856	1.17135
beta_2	1.54977	0.111288

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	beta_0	beta_1	beta_2
var_const	1	-9.3e-008	-1.e-007	1e-007
beta_0	-9.3e-008	1	-0.67	0.57
beta_1	-1.e-007	-0.67	1	-0.98
beta_2	1e-007	0.57	-0.98	1

Model Descriptions for likelihoods calculate
Model A1: $Y_{ij} = \mu(i) + e(ij)$
 $\text{Var}\{e(ij)\} = \sigma^2$

Model A2: $Y_{ij} = \mu(i) + e(ij)$
 $\text{Var}\{e(ij)\} = \sigma^2$

Model R: $Y_i = \mu + e(i)$
 $\text{Var}\{e(i)\} = \sigma^2$

Likelihoods of Interest

Model	Log(likelihood)	DF
A1	-117.994361	6
A2	-112.792067	10
fitted	-130.603483	4
R	-278.270669	2

Test 1: Does response and/or variances differ among dose levels

(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	p-value
Test 1	320.553	<.00001
Test 2	10.4046	0.03414
Test 3	25.2182	<.00001

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

The p-value for Test 2 is less than .05. Variances may not be homogeneous

The p-value for Test 3 is less than .05. You may want to try a different model

Benchmark Dose Computation

Specified effect = 0.448000 incorrect BMR, but fit not sig anyway

Risk Type = Added response

Confidence level = 0.95000

BMD = 0.021693

BMDL = 0.019826

Power Model to T3
 Input Data File: PNDT3.SET
 Thu Oct 15 09:22:54 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[dose] = control + slope * dose^{power}$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

The sign of the slope is not restricted

Total number of dose groups = 5

Total number of records with missing values = 0

Default Initial Parameter Values

var_const = 32.0509

control = 87.97

slope = -12.9239

power = 0.680847

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	120.528	23.3322
control	91.1346	2.54297
slope	-23.7298	1.84275
power	0.387245	0.0499728

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	control	slope	power
var_const	1	0.025	-0.038	-0.11
control	0.025	1	-0.81	-0.23
slope	-0.038	-0.81	1	0.35
power	-0.11	-0.23	0.35	1

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma^2$

Model A2: $Y_{ij} = \mu_i + e_{ij}$

$$\text{Var}\{e_{ij}\} = \sigma^2$$

Model R: $Y_i = \mu_i + e_i$
 $\text{Var}\{e_i\} = \sigma^2$

Likelihoods of Interest

Model	Log(Likelihood)	DF	AIC
A1	-117.994361	6	-123.994361
A2	-112.792067	10	-122.792067
fitted	-156.380933	4	-160.380933
R	-278.270669	2	-280.270669

Test 1: Does response and/or variances differ among Dose levels

(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	p-value
Test 1	320.553	<.00001
Test 2	10.4046	0.03414
Test 3	76.7731	<.00001

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

The p-value for Test 2 is less than .05. Variances may not be

homogeneous

The p-value for Test 3 is less than .05. You may want to try a different model

Benchmark Dose Computation

Specified effect = 8.797000

Risk Type = Added response

Confidence level = 0.950000

BMD = 0.077111

BMDL = 0.014861

fit not stat sig.

Power Model to LN(T3) -- not sig fit.
Input Data File: PNDT3.SET

Thu Oct 15 09:26:32 1998

BMDS MODEL RUN

The form of the response function is:

$Y[dose] = control + slope * dose^{power}$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

The sign of the slope is not restricted

Total number of dose groups = 5

Total number of records with missing values = 0

Default Initial Parameter Values
 var_const = 0.00741324
 control = 4.475
 slope = -0.1791
 power = 0.763387

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.0350098	0.00677838
control	4.53234	0.0427171
slope	-0.381831	0.0299965
power	0.406755	0.0511618

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	control	slope	power
var_const	1	0.026	-0.04	-0.11
control	0.026	1	-0.8	-0.24
slope	-0.04	-0.8	1	0.36
power	-0.11	-0.24	0.36	1

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu(i) + e(ij)$
 $\text{Var}\{e(ij)\} = \sigma^2$

Model A2: $Y_{ij} = \mu(i) + e(ij)$
 $\text{Var}\{e(ij)\} = \sigma^2(i)^2$

Model R: $Y_i = \mu + e(i)$
 $\text{Var}\{e(i)\} = \sigma^2$

Likelihoods of Interest

Model	Log(Likelihood)	DF	AIC
A1	108.044571	6	102.044571
A2	108.838261	10	98.838261
fitted	63.507442	4	59.507442
R	-58.025370	2	-60.025370

Test 1: Does response and/or variances differ among Dose levels
 (A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	p-value
Test 1	332.14	<.00001
Test 2	1.58738	0.8111
Test 3	89.0743	<.00001

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

The p-value for Test 3 is less than .05. You may want to try a different model

Benchmark Dose Computation
 Specified effect = 0.105300
 Risk Type = Added response
 Confidence level = 0.950000
 BMD = 0.042133
 BMDL = 0.008527

 Polynomial Model to ln(t3) data - poor.non-monotonic fit
 Input Data File: PNNDT3.SET

Thu Oct 15 09:27:43 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[\text{dose}] = \beta_0 + \beta_1 \cdot \text{dose} + \beta_2 \cdot \text{dose}^2 + \dots$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

Signs of the polynomial coefficients are not restricted

Total number of dose groups = 5

Total number of records with missing values = 0

Default Initial Parameter Values

var_const =	0.00741324
beta_0 =	4.52438
beta_1 =	-0.339991
beta_2 =	0.0251613

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.0134345	0.00258548
beta_0	4.5257	0.0246576
beta_1	-0.345323	0.0199328
beta_2	0.0256878	0.00189378

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	beta_0	beta_1	beta_2
var_const	1	5.4e-006	-6e-006	6.1e-006
beta_0	5.4e-006	1	-0.67	0.57
beta_1	-6e-006	-0.67	1	-0.98
beta_2	6.1e-006	0.57	-0.98	1

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu(i) + e(ij)$
 $\text{Var}\{e(ij)\} = \sigma^2$

Model A2: $Y_{ij} = \mu(i) + e(ij)$

$$\text{Var}\{e(ij)\} = \sigma^2$$

Model R: $Y_{ij} = \mu + e(i)$
 $\text{Var}\{e(i)\} = \sigma^2$

Likelihoods of Interest

Model	Log(likelihood)	DF
A1	108.044571	6
A2	108.838261	10
fitted	89.367996	4
R	-58.025370	2

Test 1: Does response and/or variances differ among dose levels

(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	p-value
Test 1	332.14	<.00001
Test 2	1.58738	0.8111
Test 3	37.3531	<.00001

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

The p-value for Test 3 is less than .05. You may want to try a different model

Benchmark Dose Computation

Specified effect = 0.105400

Risk Type = Added response

Confidence level = 0.950000

BMD = 0.312485

BMDL = 0.284691

Linear Model to T4
Input Data File: PNDST4.SET
Fri Nov 13 09:16:15 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[dose] = \beta_0 + \beta_1 * dose + \beta_2 * dose^2 + \dots$$

Dependent variable - MEAN

Independent variable - dose

var_power is set to 0

Signs of the polynomial coefficients are not restricted

Total number of dose groups - 5

Total number of records with missing values - 0

Default Initial Parameter Values

var_const	-	0.0881777
beta_0	-	3.24344
beta_1	-	-0.080935

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.109309	0.0197927
beta_0	3.2588	0.0523033
beta_1	-0.0821539	0.0112817

Asymptotic Correlation Matrix of Parameter

Estimates

	var_const	beta_0	beta_1
var_const	1	-1.5e-008	3.3e-009
beta_0	-1.5e-008	1	-0.59
beta_1	3.3e-009	-0.59	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	15	3.409	0.370	3.259	0.109
0.1000	11	3.318	0.312	3.251	0.109
1.0000	12	3.137	0.274	3.177	0.109
3.0000	11	2.680	0.255	3.012	0.109
10.0000	12	2.532	0.228	2.437	0.109

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma^2$

Model A2: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma_i^2$

Model R: $Y_i = \mu_i + e_i$
 $\text{Var}\{e_i\} = \sigma^2$

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	46.674670	6	40.674670
A2	48.143903	10	38.143903
fitted	37.014092	3	34.014092
R	-73.762023	2	-75.762023

Test 1: Does response and/or variances differ among dose levels

(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	p-value
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Test 1	240.873	<.00001
Test 2	2.93847	0.5682
Test 3	19.3212	0.0002346

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

The p-value for Test 3 is less than .05. You may want to try a different model

Benchmark Dose Computation

Specified effect = 0.341000

Risk Type = Added response

Confidence level = 0.950000

BMD = 4.150748

BMDL = 3.380265

p = 0.0002; fit is not significant

Polynomial Model of T4 Dev NT, PND5.
 Input Data File: PNDST4.SET
 Fri Nov 13 09:19:22 1998

0.0000	15	3.409	0.370	3.390	0.081
0.1000	11	3.318	0.312	3.363	0.081
1.0000	12	3.137	0.274	3.135	0.081
3.0000	11	2.680	0.255	2.752	0.081
10.0000	12	2.532	0.228	2.743	0.081

BMDS MODEL RUN

The form of the response function is:

$$Y[\text{dose}] = \text{beta_0} + \text{beta_1} * \text{dose} + \text{beta_2} * \text{dose}^2 \\ + \dots$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

Signs of the polynomial coefficients are not restricted

Total number of dose groups = 5

Total number of records with missing values = 0

Default Initial Parameter Values

var_const =	0.0881777
beta_0 =	3.38653
beta_1 =	-0.295565
beta_2 =	0.0210057

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.0814824	0.0147541
beta_0	3.39012	0.0535444
beta_1	-0.297199	0.0481122
beta_2	0.0211338	0.00463037

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	beta_0	beta_1	beta_2
var_const	1	1.4e-008	-1.6e-008	
beta_0	1.4e-008	1	-0.63	0.54
beta_1	-1.6e-008	-0.63	1	-0.98
beta_2	1.7e-008	0.54	-0.98	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu_{(i)} + e_{(ij)}$
 $\text{Var}\{e_{(ij)}\} = \sigma^2$

Model A2: $Y_{ij} = \mu_{(i)} + e_{(ij)}$
 $\text{Var}\{e_{(ij)}\} = \sigma_{(i)}^2$

Model R: $Y_i = \mu + e_i$
 $\text{Var}\{e_i\} = \sigma^2$

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	46.674670	6	40.674670
A2	48.143903	10	38.143903
fitted	45.974719	4	41.974719
R	-73.762023	2	-75.762023

Test 1: Does response and/or variances differ among dose levels
 (A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	p-value
Test 1	240.873	<.00001
Test 2	2.93847	0.5682
Test 3	1.3999	0.4966

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

Benchmark Dose Computation

Specified effect = 0.341000

Risk Type = Added response

Confidence level = 0.950000

BMD = 1.260331

BMDL = 0.976425

Test 3 p= 0.4966 good fit but non-monotonic

Power Model to T4 fit is not statistically sig., though looks good
Input Data File: PNDST4.SET
Thu Oct 15 09:06:00 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[\text{dose}] = \text{control} + \text{slope} * \text{dose}^{\text{power}}$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

The sign of the slope is not restricted

Total number of dose groups = 5

Total number of records with missing values = 0

Default Initial Parameter Values

var_const	=	0.0881777
control	=	3.409
slope	=	-0.3073
power	=	0.522057

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.0880759	0.0159627
control	3.43182	0.0600052
slope	-0.383362	0.0458711
power	0.393979	0.0860983

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	control	slope	power
var_const	1	0.01	-0.016	-0.043
control	0.01	1	-0.77	-0.24
slope	-0.016	-0.77	1	0.36
power	-0.043	-0.24	0.36	1

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu_{(i)} + e_{(ij)}$
 $\text{Var}\{e_{(ij)}\} = \sigma^2$

Model A2: $Y_{ij} = \mu_{(i)} + e_{(ij)}$

$$\text{Var}\{e_{(ij)}\} = \sigma^2$$

Model R: $Y_{ij} = \mu_{(i)} + e_{(ij)}$
 $\text{Var}\{e_{(ij)}\} = \sigma^2$

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	46.674670	6	40.674670
A2	48.143903	10	38.143903
fitted	43.601455	4	39.601455
R	-77.447490	2	-79.447490

Test 1: Does response and/or variances differ among Dose levels

(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	p-value
Test 1	248.244	<.00001
Test 2	2.93847	0.5682
Test 3	6.14643	0.04627

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

The p-value for Test 3 is less than .05. You may want to try a different model

Benchmark Dose Computation

Specified effect = 0.341000

Risk Type = Added response

Confidence level = 0.950000

BMD = 0.742881

BMDL = 0.054831

Test 3 p=0.04627 fit is not significant

Power Model to ln(T4) data; fit not sig. though visually compelling

Input Data File: PNDST4.SET

Thu Oct 15 09:09:38 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[\text{dose}] = \text{control} + \text{slope} * \text{dose}^{\text{power}}$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

The sign of the slope is not restricted

Total number of dose groups = 5

Total number of records with missing values = 0

Default Initial Parameter Values

var_const = 0.00947493

control = 1.221

slope = -0.0947234

power = 0.560275

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.00952729	0.00172675
control	1.22908	0.019429
slope	-0.121685	0.0142549
power	0.419862	0.0855506

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	control	slope	power
var_const	1	0.01	-0.016	-0.043
control	0.01	1	-0.76	-0.24
slope	-0.016	-0.76	1	0.38
power	-0.043	-0.24	0.38	1

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu(i) + e(ij)$
 $\text{Var}\{e(ij)\} = \sigma^2$

Model A2: $Y_{ij} = \mu(i) + e(ij)$
 $\text{Var}\{e(ij)\} = \sigma^2$

Model R: $Y_i = \mu + e(i)$
 $\text{Var}\{e(i)\} = \sigma^2$

Likelihoods of Interest

Model	Log(Likelihood)	DF	AIC
A1	114.711161	6	108.711161
A2	114.807881	10	104.807881
fitted	111.434649	4	107.434649
R	-10.528288	2	-12.528288

Test 1: Does response and/or variances differ among Dose levels
(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	p-value
Test 1	250.479	<.00001
Test 2	0.193439	0.9956
Test 3	6.55302	0.03776

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

The p-value for Test 3 is less than .05. You may want to try a different model

Benchmark Dose Computation

Specified effect = 0.105400

Risk Type = Added response

Confidence level = 0.950000

BMD = 0.710206

BMDL = 0.160220

Test 3 p= 0.03776 fit is not sig

Polynomial Model to ln(T4) data: good fit but non-monotonic

Input Data File: PNDST4.SET
Thu Oct 15 09:12:44 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[\text{dose}] = \beta_0 + \beta_1 \cdot \text{dose} + \beta_2 \cdot \text{dose}^2 + \dots$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

Signs of the polynomial coefficients are not restricted

Total number of dose groups = 5

Total number of records with missing values = 0

Default Initial Parameter Values

var_const =	0.00947493
beta_0 =	1.21703
beta_1 =	-0.0969813
beta_2 =	0.00677454

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.00876836	0.0015877
beta_0	1.21782	0.0175647
beta_1	-0.0972186	0.0157828
beta_2	0.00679059	0.00151895

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	beta_0	beta_1	beta_2
var_const	1	1.9e-008	-2.9e-008	2.9e-008
beta_0	1.9e-008	1	-0.63	0.54
beta_1	-2.9e-008	-0.63	1	-0.98
beta_2	2.9e-008	0.54	-0.98	1

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu(i) + e(ij)$
 $\text{Var}\{e(ij)\} = \sigma^2$

Model A2: $Y_{ij} = \mu(i) + e(ij)$

$$\text{Var}\{e(ij)\} = \sigma^2$$

Model R: $Y_{ij} = \mu + e(i)$
 $\text{Var}\{e(i)\} = \sigma^2$

Likelihoods of Interest

Model	Log(likelihood)	DF
A1	114.711161	6
A2	114.807881	10
fitted	113.966479	4
R	-10.528288	2

Test 1: Does response and/or variances differ among dose levels

(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs. A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	p-value
Test 1	250.479	<.00001
Test 2	0.193439	0.9956
Test 3	1.48936	0.4749

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

Benchmark Dose Computation

Specified effect = 0.105400
Risk Type = Added response
Confidence level = 0.950000
BMD = 1.181691
BMDL = 0.916642

Test 3 p = 0.4749 good fit but non-monotonic

Linear Model to ln(t4) not sig fit.
Input Data File: PNDST4.SET

Thu Oct 15 09:15:30 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[dose] = \beta_0 + \beta_1 * dose + \beta_2 * dose^2 + \dots$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

Signs of the polynomial coefficients are not restricted

Total number of dose groups = 5

Total number of records with missing values = 0

Default Initial Parameter Values

var_const = 0.00947493

beta_0 = 1.17089

beta_1 = -0.0277611

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.0116412	0.0021079
beta_0	1.17562	0.0170687
beta_1	-0.0281216	0.00368168

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	beta_0	beta_1
var_const	1	1.3e-007	-2.2e-007
beta_0	1.3e-007	1	-0.59
beta_1	-2.2e-007	-0.59	1

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu(i) + e(ij)$
 $\text{Var}\{e(ij)\} = \sigma^2$

Model A2: $Y_{ij} = \mu(i) + e(ij)$
 $\text{Var}\{e(ij)\} = \sigma^2(i)$

Model R: $Y_i = \mu + e(i)$

$$\text{Var}\{e(i)\} = \sigma^2$$

Likelihoods of Interest

Model	Log(Likelihood)	DF
A1	114.711161	6
A2	114.807881	10
fitted	105.322652	3
R	-10.528288	2

Test 1: Does response and/or variances differ among dose levels

(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	p-value
Test 1	250.479	<.00001
Test 2	0.193439	0.9956
Test 3	18.777	0.000304

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

The p-value for Test 3 is less than .05. You may want to try a different model

Benchmark Dose Computation

Specified effect = 0.105400

Risk Type = Added response

Confidence level = 0.950000

BMD = 3.748015

BMDL = 3.077655

Morphometry

Polynomial Model to morphometry
 Input Data File: PND5MORPH.SET
 Fri Nov 13 09:25:09 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[dose] = \beta_0 + \beta_1 * dose + \beta_2 * dose^2 + \dots$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

Signs of the polynomial coefficients are not restricted

Total number of dose groups = 5

Total number of records with missing values = 0

Default Initial Parameter Values

var_const =	7719.92
beta_0 =	297.226
beta_1 =	-32.7095
beta_2 =	2.40589

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	7580.83	1072.09
beta_0	297.226	13.7572
beta_1	-32.7095	11.6835
beta_2	2.40589	1.11056

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	beta_0	beta_1	beta_2
var_const	1	-1.2e-007	-6.5e-009	-3.1e-009
beta_0	-1.2e-007	1	-0.69	0.6
beta_1	-6.5e-009	-0.69	1	-0.98
beta_2	-3.1e-009	0.6	-0.98	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	20	317.833	66.647	297.226	7580.830
0.3000	20	259.854	51.055	288.351	7580.830
1.0000	20	272.991	112.649	269.328	7580.830
3.0000	20	221.999	97.288	227.968	7580.830
10.0000	20	210.571	96.935	234.778	7580.830

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu(i) + e(ij)$
 $\text{Var}\{e(ij)\} = \sigma^2$

Model A2: $Y_{ij} = \mu(i) + e(ij)$
 $\text{Var}\{e(ij)\} = \sigma^2(i)$

Model R: $Y_i = \mu + e(i)$
 $\text{Var}\{e(i)\} = \sigma^2$

Likelihoods of Interest

Model	Log(Likelihood)	DF	AIC
A1	-495.013276	6	-501.013276
A2	-487.601467	10	-497.601467
fitted	-496.668887	4	-500.668887
R	-684.899906	2	-686.899906

Test 1: Does response and/or variances differ among dose levels

(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood.Ratio)	p-value
Test 1	379.773	<.00001
Test 2	14.8236	0.005081
Test 3	3.31122	0.191

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

The p-value for Test 2 is less than .05. Variances may not be homogeneous

Benchmark Dose Computation

Specified effect = 31.780000

Risk Type = Added response

Confidence level = 0.950000

BMD = 1.053164

BMDL = 0.643849

p = 0.19; Fit is significant, though estimate of control value is somewhat low.

Power Model of morphometry data BMR: ctl-10% of ctl:

Fit is good, but BMD values might be iffy.

Input Data File: PNDSMORPH.SET

Mon Oct 19 09:42:27 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[dose] = control + slope * dose^{power}$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

The sign of the slope is not restricted

Total number of dose groups = 5

Total number of records with missing values = 0

Default Initial Parameter Values

var_const = 7719.92

control = 317.833

slope = -63.6618

power = 0.221549

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	7461.41	1055.21
control	317.54	16.9775
slope	-63.9964	15.6683
power	0.233056	0.19593

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	control	slope	power
var_const	1	-0.0005	0.00084	0.0031
control	-0.0005	1	-0.86	-0.16
slope	0.00084	-0.86	1	0.27
power	0.0031	-0.16	0.27	1

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu(i) + e(ij)$
 $\text{Var}\{e(ij)\} = \sigma^2$

Model A2: $Y_{ij} = \mu(i) + e(ij)$
 $\text{Var}\{e(ij)\} = \sigma^2(i)$

Model R: $Y_i = \mu + e(i)$
 $\text{Var}\{e(i)\} = \sigma^2$

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-495.013276	6	-501.013276
A2	-487.601467	10	-497.601467
fitted	-495.874987	4	-499.874987
R	-684.899987	2	-686.899987

Test 1: Does response and/or variances differ among Dose levels
(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	p-value
Test 1	379.773	<.00001
Test 2	14.8236	0.005081
Test 3	1.72342	0.4224

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

The p-value for Test 2 is less than .05. Variances may not be homogeneous

Benchmark Dose Computation

Specified effect = 31.780000

Risk Type = Added response

Confidence level = 0.950000

BMD = 0.049612

BMDL = 0.000053

BMDL curve computation failed for BMR = -40.223063 .

The BMDL curve appearing in the graph may not be accurate.

BMDL curve computation failed for BMR = -53.630750 .

The BMDL curve appearing in the graph may not be accurate.

Power Model of In morphometry data: BMDL interval incl. 0.
 Input Data File: PND5LNMRPH.SET
 Mon Oct 19 10:39:36 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[\text{dose}] = \text{control} + \text{slope} * \text{dose}^{\text{power}}$$

Dependent variable - MEAN

Independent variable - dose

var_power is set to 0

The sign of the slope is not restricted

Total number of dose groups = 5

Total number of records with missing values = 0

Default Initial Parameter Values

var_const	=	0.10469
control	=	5.7398
slope	=	-0.278833
power	=	0.207251

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.101337	0.0143325
control	5.73489	0.0602424
slope	-0.270661	0.0560389
power	0.243809	0.16517

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	control	slope	power
var_const	1	-0.0033	0.0045	0.013
control	-0.0033	1	-0.85	-0.25
slope	0.0045	-0.85	1	0.34
power	0.013	-0.25	0.34	1

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu(i) + e(ij)$
 $\text{Var}\{e(ij)\} = \sigma^2$

Model A2: $Y_{ij} = \mu(i) + e(ij)$

$$\text{Var}\{e(ij)\} = \sigma^2$$

Model R: $Y_i = \mu + e(i)$
 $\text{Var}\{e(i)\} = \sigma^2$

Likelihoods of Interest

Model	Log(Likelihood)	DF	AIC
A1	65.402082	6	59.402082
A2	74.707982	10	64.707982
fitted	64.465206	4	60.465206
R	-127.966330	2	-129.966330

Test 1: Does response and/or variances differ among Dose levels

(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test -2*log(Likelihood Ratio) p-value

Test 1	386.737	<.00001
Test 2	18.6118	0.0009367
Test 3	1.87375	0.3918

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

The p-value for Test 2 is less than .05. Variances may not be homogeneous

Benchmark Dose Computation

Specified effect = 0.105400

Risk Type = Added response

Confidence level = 0.950000

BMD = 0.020896

BMDL computation failed. Lower limit includes zero.

Polynomial Model to Ln morphometry data:
Fit is good, but non-monotonicity is present as in
all of these quadratic fits.
Input Data File: PNDSLNMNRPH.SET
Mon Oct 19 10:36:23 1998
BMDS MODEL RUN

The form of the response function is:

$$Y[\text{dose}] = \beta_0 + \beta_1 \cdot \text{dose} + \beta_2 \cdot \text{dose}^2 + \dots$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

Signs of the polynomial coefficients are not restricted

Total number of dose groups = 5

Total number of records with missing values = 0

Default Initial Parameter Values

var_const = 0.10469

beta_0 = 5.65407

beta_1 = -0.136165

beta_2 = 0.00973242

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.102833	0.0145428
beta_0	5.65407	0.0483604
beta_1	-0.136165	0.041375
beta_2	0.00973241	0.00396184

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	beta_0	beta_1	beta_2
var_const	1	2.3e-006	-6.9e-007	-3.8e-007
beta_0	2.3e-006	1	-0.65	0.56
beta_1	-6.9e-007	-0.65	1	-0.98
beta_2	-3.8e-007	0.56	-0.98	1

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu(i) + e(ij)$
 $\text{Var}\{e(ij)\} = \sigma^2$

Model A2: $Y_{ij} = \mu(i) + e(ij)$
 $\text{Var}\{e(ij)\} = \sigma^2(i)$

Model R: $Y_i = \mu + e(i)$

$$\text{Var}\{e(i)\} = \sigma^2$$

Likelihoods of Interest

Model	Log(likelihood)	DF
A1	65.402082	6
A2	74.707982	10
fitted	63.732271	4
R	-127.966330	2

Test 1: Does response and/or variances differ among dose levels
(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	p-value
Test 1	386.737	<.00001
Test 2	18.6118	0.0009367
Test 3	3.33962	0.1883

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels
The p-value for Test 2 is less than .05. Variances may not be homogeneous

Benchmark Dose Computation

Specified effect = 0.105400

Risk Type = Added response

Confidence level = 0.950000

BMD = 0.822403

BMDL = 0.537758

Dev NT, 14 day Motor activity

Linear Model to movement data, BMR 0.90 CTL
 Input Data File: PND5MOT.SET
 Fri Nov 13 10:06:28 1998

BMD5 MODEL RUN

The form of the response function is:

$$Y[\text{dose}] = \beta_0 + \beta_1 \cdot \text{dose} + \beta_2 \cdot \text{dose}^2 + \dots$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

Signs of the polynomial coefficients are not restricted

Total number of dose groups = 5

Total number of records with missing values = 0

Default Initial Parameter Values

var_const =	62118.5
beta_0 =	288.171
beta_1 =	12.5918

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	59798.8	8456.83
beta_0	288.171	30.6017
beta_1	12.5918	6.524

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	beta_0	beta_1
var_const	1	-1.6e-009	-4.1e-011
beta_0	-1.6e-009	1	-0.6
beta_1	-4.1e-011	-0.6	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	20	244.050	162.753	288.171	59798.808
0.1000	20	313.400	177.250	289.430	59798.808
1.0000	20	295.650	264.137	300.763	59798.808
3.0000	20	361.650	295.060	325.947	59798.808
10.0000	20	403.650	309.609	414.089	59798.808

Model A1: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma^2$

Model A2: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma^2(i)$

Model R: $Y_i = \mu + e_i$
 $\text{Var}\{e_i\} = \sigma^2$

Likelihoods of Interest

Model	Log(Likelihood)	DF	AIC
A1	-599.275307	6	-605.275307
A2	-592.810370	10	-602.810370
fitted	-599.937050	3	-602.937050
R	-782.524296	2	-784.524296

Test 1: Does response and/or variances differ among dose levels

(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	p-value
Test 1	366.498	<.00001
Test 2	12.9299	0.01162
Test 3	1.32349	0.7236

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

The p-value for Test 2 is less than .05. Variances may not be homogeneous

Benchmark Dose Computation

Specified effect = 24.450000
 Risk Type = Added response
 Confidence level = 0.950000
 BMD = 1.941733
 BMDL = 1.044402
 p = 0.7236: fit is significant

Model Descriptions for likelihoods calculated

Polynomial Model to Dev NT. Motor Activity.
Movement data
Input Data File: PNDSMOT.SET
Fri Nov 13 10:13:17 1998

BMDS MODEL RUN**The form of the response function is:**

$$Y[\text{dose}] = \beta_0 + \beta_1 \cdot \text{dose} + \beta_2 \cdot \text{dose}^2 + \dots$$

Dependent variable = MEAN**Independent variable = dose****var_power is set to 0****Signs of the polynomial coefficients are not restricted****Total number of dose groups = 5****Total number of records with missing values = 0**

Default Initial Parameter Values
var_const = 62118.5
beta_0 = 273.043
beta_1 = 35.2836
beta_2 = -2.22083

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	59475.7	8411.3
beta_0	273.043	36.7784
beta_1	35.2836	31.466
beta_2	-2.22083	3.013

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	beta_0	beta_1	beta_2
var_const	1	-1.6e-008	-1.2e-009	-4.2e-010
beta_0	-1.6e-008	1	-0.65	0.56
beta_1	-1.2e-009	-0.65	1	-0.98
beta_2	-4.2e-010	0.56	-0.98	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	20	244.050	162.753	273.043	59475.683
0.1000	20	313.400	177.250	276.327	59475.683
1.0000	20	295.650	264.137	303.885	59475.683
3.0000	20	361.650	295.060	352.244	59475.683
10.0000	20	403.650	309.609	381.588	59475.683

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu_i + e_{ij}$
Var{e_{ij}} = \sigma^2

Model A2: $Y_{ij} = \mu_i + e_{ij}$
Var{e_{ij}} = \sigma_i^2

Model R: $Y_i = \mu + e_i$
Var{e_i} = \sigma^2

Likelihoods of Interest

Model	Log(Likelihood)	DF	AIC
A1	-599.275307	6	-605.275307
A2	-592.810370	10	-602.810370
fitted	-599.666141	4	-603.666141
R	-782.524296	2	-784.524296

Test 1: Does response and/or variances differ among dose levels

(A2 vs. R)**Test 2: Are Variances Homogeneous (A1 vs A2)****Test 3: Does the Model for the Mean Fit (A1 vs. fitted)****Tests of Interest**

Test	-2*log(Likelihood Ratio)	p-value
Test 1	366.498	<.00001
Test 2	12.9299	0.01162
Test 3	0.781668	0.6765

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

The p-value for Test 2 is less than .05. Variances may not be homogeneous

Benchmark Dose Computation
Specified effect = 24.400000
Risk Type = Added response
Confidence level = 0.950000
BMD = 0.724586
BMDL = 0.286056
p = 0.68: fit is significant

Linear Model Dev NT, 14 day, Mot Act/ Time
 Input Data File: PND5MOT.SET
 Fri Nov 13 10:17:33 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[dose] = \beta_0 + \beta_1 * dose + \beta_2 * dose^2 + \dots$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

Signs of the polynomial coefficients are not restricted

Total number of dose groups = 5

Total number of records with missing values = 0

Default Initial Parameter Values

var_const =	102540
beta_0 =	239.07
beta_1 =	14.0355

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	98840.4	13978.1
beta_0	239.07	39.3429
beta_1	14.0355	8.38755

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	beta_0	beta_1
var_const	1	3.1e-012	1.5e-013
beta_0	3.1e-012	1	-0.6
beta_1	1.5e-013	-0.6	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	20	186.050	184.777	239.070	98840.358
0.1000	20	267.800	229.193	240.473	98840.358
1.0000	20	238.500	277.278	253.105	98840.358
3.0000	20	337.050	437.753	281.176	98840.358
10.0000	20	363.850	396.886	379.425	98840.358

Model A1: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma^2$

Model A2: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma_i^2$

Model R: $Y_i = \mu + e_i$
 $\text{Var}\{e_i\} = \sigma^2$

Likelihoods of Interest

Model	Log(Likelihood)	DF	AIC
A1	-624.335869	6	-630.335869
A2	-614.316108	10	-624.316108
fitted	-625.063064	3	-628.063064
R	-807.202408	2	-809.202408

Test 1: Does response and/or variances differ among dose levels
 (A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	p-value
Test 1	365.733	<.00001
Test 2	20.0395	0.0004905
Test 3	1.45439	0.6928

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

The p-value for Test 2 is less than .05. Variances may not be homogeneous

Benchmark Dose Computation

Specified effect = 18.600000
 Risk Type = Added response
 Confidence level = 0.950000
 BMD = 1.325212
 BMDL = 0.666670
 p = 0.69: fit is significant

Model Descriptions for likelihoods calculated

Polynomial Model Dev NT, 14d, Motor
Activity
Input Data File: PNDSMOT.SET
Fri Nov 13 10:21:13 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[\text{dose}] = \beta_0 + \beta_1 * \text{dose} + \beta_2 * \text{dose}^2 + \dots$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

Signs of the polynomial coefficients are not restricted

Total number of dose groups = 5

Total number of records with missing values = 0

Default Initial Parameter Values

var_const	102540
beta_0	216.841
beta_1	47.3781
beta_2	-3.26322

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	98142.7	13879.5
beta_0	216.841	47.2446
beta_1	47.3781	40.4204
beta_2	-3.26322	3.87043

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	beta_0	beta_1	beta_2
var_const	1	-2.6e-010	-7.8e-011	-3.5e-011
beta_0	-2.6e-010	1	-0.65	0.56
beta_1	-7.8e-011	-0.65	1	-0.98
beta_2	-3.5e-011	0.56	-0.98	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	20	186.050	184.777	216.841	98142.713
0.1000	20	267.800	229.193	221.220	98142.713
1.0000	20	238.500	277.278	257.693	98142.713
3.0000	20	337.050	437.753	319.817	98142.713
10.0000	20	363.850	396.886	331.668	98142.713

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma^2$

Model A2: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma_i^2$

Model R: $Y_i = \mu + e_i$
 $\text{Var}\{e_i\} = \sigma^2$

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-624.335869	6	-630.335869
A2	-614.316108	10	-624.316108
fitted	-624.708897	4	-628.708897
R	-807.202408	2	-809.202408

Test 1: Does response and/or variances differ among dose levels

(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	p-value
Test 1	365.733	<.00001
Test 2	20.0395	0.0004905
Test 3	0.746057	0.6886

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

The p-value for Test 2 is less than .05. Variances may not be homogeneous

Benchmark Dose Computation

Specified effect = 18.600000
Risk Type = Added response
Confidence level = 0.950000
BMD = 0.403818
BMDL = 0.164887
p = 0.69: fit is significant

Standard Histopathology, PNDS

=====
Gamma Model
 Input Data File: PNDSSH.SET

Wed Dec 02 09:12:32 1998

BMDS MODEL RUN

The form of the probability function is:

P[response]=
 background+(1-background)*CumGamma[slope*dose,pow
 er],

where CumGamma(.) is the cumulative Gamma
 distribution function

Dependent variable = incid

Independent variable = dose

Power parameter is restricted as power>=1

Total number of observations = 5

Total number of records with missing values = 0

Default Initial Parameter Values

Background = 0.25

Slope = 0.410494

Power = 1.2

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0.46658	0.103504
Slope	0.319538	0.674456
Power	1	1.69734

**Asymptotic Correlation Matrix of Parameter
 Estimates**

	Background	Slope	Power
Background	1	0.3969	0.5033
Slope	0.3969	1	0.9745
Power	0.5033	0.9745	1

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	DF	P-value
Full model	-28.7724			
Fitted model	-32.1006	6.65634	2	0.0358586
Reduced model	-38.1909	12.1806	2	0.0022647

Goodness of Fit

Dose	Est_Prob.	Expected	Observed	Size
0.0000	0.4666	5.599	3	12
0.1000	0.4834	5.800	8	12
1.0000	0.6125	7.350	9	12
3.0000	0.7955	9.546	8	12
10.0000	0.9782	11.738	12	12

Chi-square = 6.32 DF = 2 P-value = 0.0423

Benchmark Dose Computation

Specified effect = 0.100000

Risk Type = Extra risk

Confidence level = 0.950000

BMD = 0.329728

BMDL = 0.1702

Chi-square = 6.32 DF = 2 P-value = 0.0423

Logistic Model
Input Data File: PND5SH.SET

Wed Dec 02 09:27:52 1998

BMDS MODEL RUN

The form of the probability function is:

$$P[\text{response}] = 1/[1+\text{EXP}(-\text{intercept}-\text{slope}*\text{dose})]$$

Dependent variable = incid

Independent variable = dose

Slope parameter is not restricted

Total number of observations = 5

Total number of records with missing values = 0

Default Initial Parameter Values

intercept = -0.101596

slope = 0.460241

Parameter Estimates

Variable	Estimate	Std. Err.
intercept	-0.0560692	0.415842
slope	0.427692	0.117106

Asymptotic Correlation Matrix of Parameter Estimates

	intercept	slope
intercept	1	-0.3488
slope	-0.3488	1

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	DF	P-value
Full model	-28.7724			
Fitted model	-32.0759	6.60704	3	0.0855353
Reduced model	-38.1909	12.2299	1	0.0004703

Goodness of Fit					
Dose	Est. Prob.	Expected	Observed	Size	
0.0000	0.4860	5.832	3	12	
0.1000	0.4967	5.960	8	12	
1.0000	0.5919	7.102	9	12	
3.0000	0.7733	9.280	8	12	
10.0000	0.9855	11.826	12	12	

Chi-square = 6.26 DF = 2 P-value = 0.0437

Benchmark Dose Computation
Specified effect = 0.100000
Risk Type = Extra risk
Confidence level = 0.950000
BMD = 0.481420
BMDL = 0.4807

Chi-square = 6.26 DF = 2 P-value = 0.0437

Reduced model	-38.1909	12.4419	1
	0.00041981		

Probit Model
Input Data File: PND5SH.SET

Wed Dec 02 09:30:08 1998

BMDS MODEL RUN

The form of the probability function is:

$P[\text{response}] = \text{CumNorm}(\text{Intercept} + \text{Slope} * \text{Dose})$,

where $\text{CumNorm}(.)$ is the cumulative normal distribution function

Dependent variable = incid

Independent variable = dose

Slope parameter is not restricted

Total number of observations = 5

Total number of records with missing values = 0

Default Initial Parameter Values

Intercept = -0.0379013

Slope = 0.257033

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size
0.0000	0.4901	5.882	3	12
0.1000	0.5000	6.000	8	12
1.0000	0.5878	7.053	9	12
3.0000	0.7627	9.152	8	12
10.0000	0.9927	11.912	12	12

Chi-square = 6.11 DF = 2 P-value = 0.0472

Benchmark Dose Computation

Specified effect = 0.100000

Risk Type = Extra risk

Confidence level = 0.950000

BMD = 0.519124

BMDL = 0.5165

Chi-square = 6.11 DF = 2 P-value = 0.0472

Parameter Estimates

Variable	Estimate	Std. Err.
Intercept	-0.0247531	0.279086
Slope	0.246554	0.111384

Asymptotic Correlation Matrix of Parameter Estimates

	Intercept	Slope
Intercept	1	-0.518
Slope	-0.518	1

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	DF	P-value
Full model	-28.7724			
Fitted model	-31.9699	6.39504	3	0.0938949

Quantal Linear Model
Input Data File: PND5SH.SET

Wed Dec 02 09:30:59 1998

BMDS MODEL RUN

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{slope} * \text{dose})]$$

Dependent variable = incid

Independent variable = dose

Total number of observations = 5

Total number of records with missing values = 0

Default Initial Parameter Values

Background = 0.25

Slope = 0.601161

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0.46658	0.13597
Slope	0.319538	0.159614

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Slope
Background	1	-0.4814
Slope	-0.4814	1

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	DF	P-value
Full model	-28.7724			
Fitted model	-32.1006	6.65634	3	0.0836966
Reduced model	-38.1909	12.1806	1	
	0.00048289			

Goodness of Fit					
Dose	Est._Prob.	Expected	Observed	Size	
0.0000	0.4666	5.599	3	12	
0.1000	0.4834	5.800	8	12	
1.0000	0.6125	7.350	9	12	
3.0000	0.7955	9.546	8	12	
10.0000	0.9782	11.738	12	12	
Chi-square = 6.32 DF = 3 P-value = 0.0969					

Benchmark Dose Computation
Specified effect = 0.100000
Risk Type = Extra risk
Confidence level = 0.950000
BMD = 0.329728
BMDL = 0.1702
Chi-square = 6.32 DF = 3 P-value = 0.0969

Goodness of Fit

Quantal Quadratic Model
Input Data File: PND5SH.SET
Wed Dec 02 09:33:47 1998

Dose	Est_Prob.	Expected	Observed	Size
0.0000	0.5337	6.405	3	12
0.1000	0.5340	6.408	8	12
1.0000	0.5580	6.696	9	12
3.0000	0.7117	8.541	8	12
10.0000	0.9978	11.973	12	12

Chi-square = 6.67 DF = 3 P-value = 0.0832

BMDS MODEL RUN

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{slope} * \text{dose}^2)]$$

Dependent variable = incid

Independent variable = dose

Total number of observations = 5

Total number of records with missing values = 0

Default Initial Parameter Values
 Background = 0.25
 Slope = 0.0770509

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0.533712	0.112476
Slope	0.0534369	0.0465538

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Slope
Background	1	-0.3763
Slope	-0.3763	1

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	DF	P-value
Full model	-28.7724			
Fitted model	-32.2465	6.94818	3	0.0735679
Reduced model	-38.1909	11.8888	1	
	0.00056474			

Fitted model	-32.1006	6.65634	2	0.0358586
Reduced model	-38.1909	12.1806	2	0.0022647

=====

Weibull Model
Input Data File: PND5SH.SET

Wed Dec 02 09:36:01 1998

=====

BMDS MODEL RUN

=====

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{slope} * \text{dose}^{\text{power}})]$$

Dependent variable = incid

Independent variable = dose

Power parameter is restricted as power >= 1

Total number of observations = 5

Total number of records with missing values = 0

Default Initial Parameter Values

Background = 0.25

Slope = 0.410494

Power = 1.2

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size
0.0000	0.4666	5.599	3	12
0.1000	0.4834	5.800	8	12
1.0000	0.6125	7.350	9	12
3.0000	0.7955	9.546	8	12
10.0000	0.9782	11.738	12	12

Chi-square = 6.32 DF = 2 P-value = 0.0423

Benchmark Dose Computation

Specified effect = 0.100000

Risk Type = Extra risk

Confidence level = 0.950000

BMD = 0.329728

BMDL = 0.1702

Chi-square = 6.32 DF = 2 P-value = 0.0423

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0.46658	0.22829
Slope	0.319538	1.04754
Power	1	1.80673

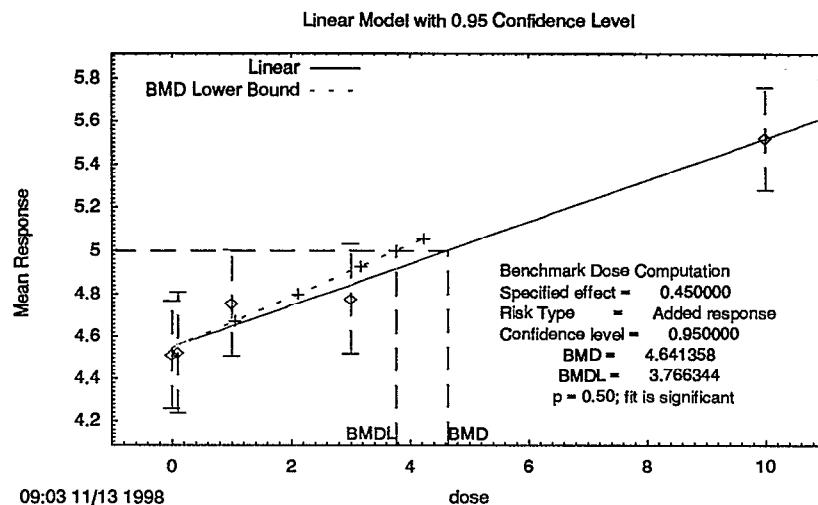
Asymptotic Correlation Matrix of Parameter Estimates

	Background	Slope	Power
Background	-1	1.134	-1.164
Slope	1.134	-1	1.012
Power	-1.164	1.012	-1

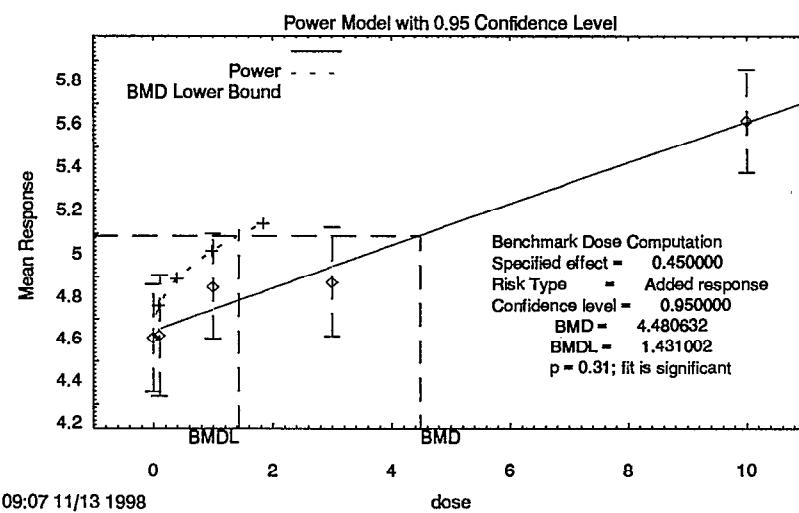
Analysis of Deviance Table

Model	Log(likelihood)	Deviance	DF	P-value
Full model	-28.7724			

Developmental Neurotoxicity, PND 5 TSH, Male and Female Combined

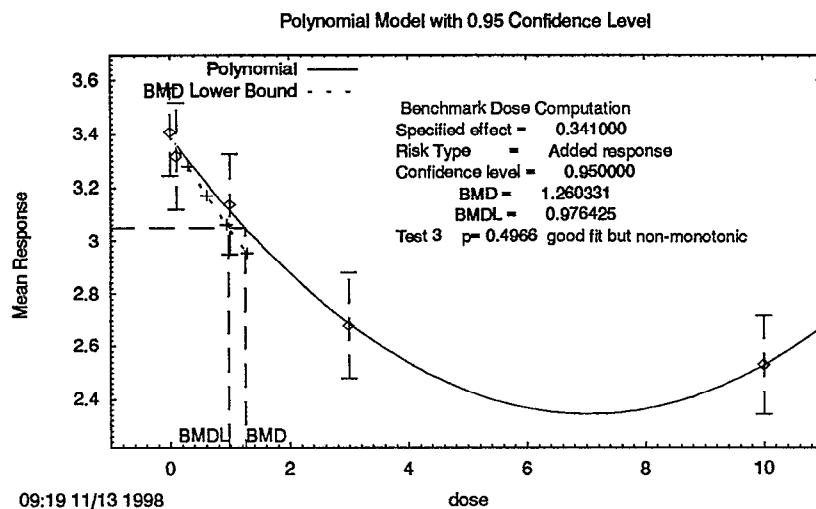


Developmental Neurotoxicity, PND 5 TSH, Male and Female Combined



Developmental Neurotoxicity, PND 5

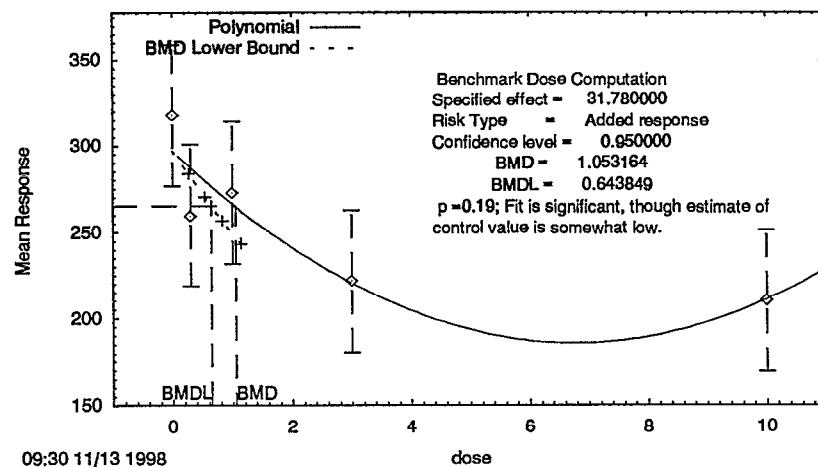
T4, Male and Female Combined



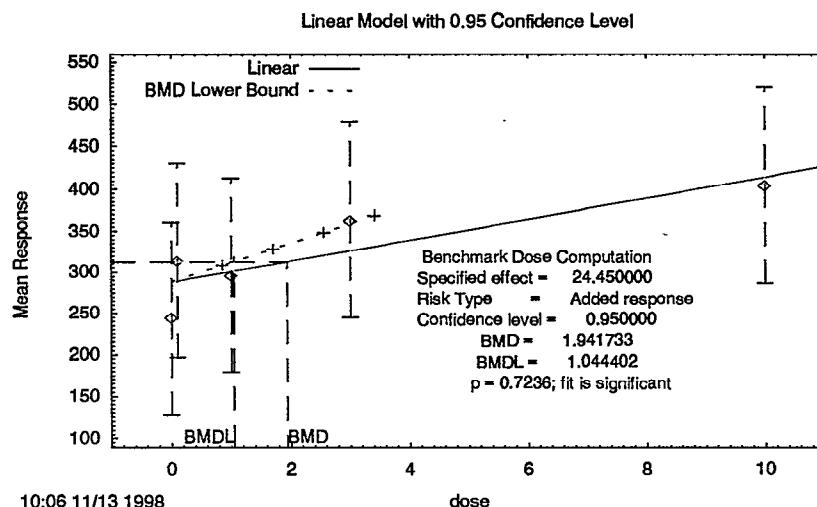
Developmental Neurotoxicity, PND 5

Morphometry, Male and Female Combined

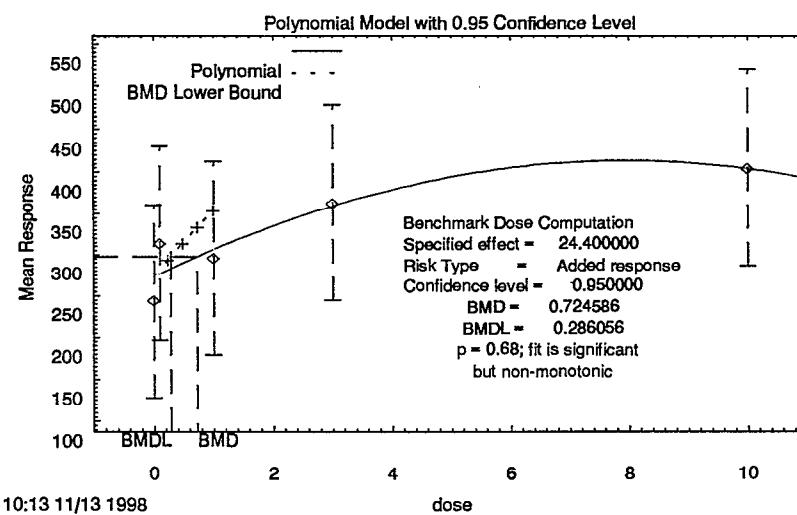
Polynomial Model with 0.95 Confidence Level



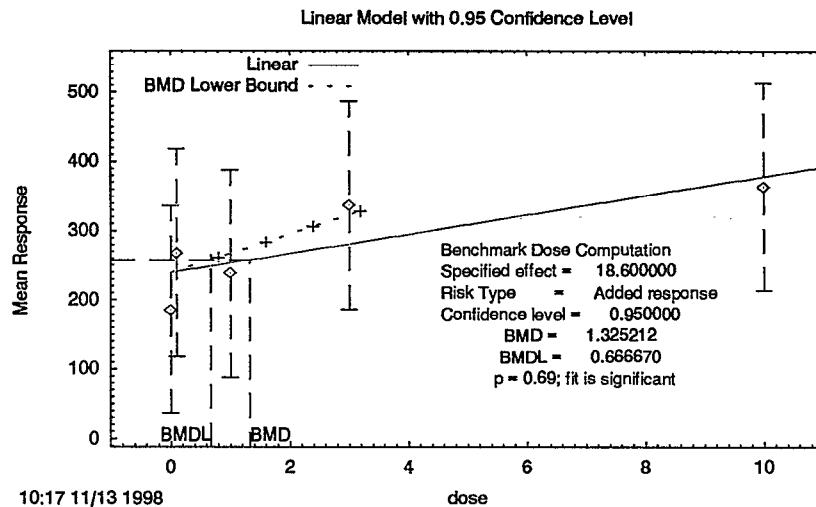
Developmental Neurotoxicity, PND 14 Motor Activity, Movement Data



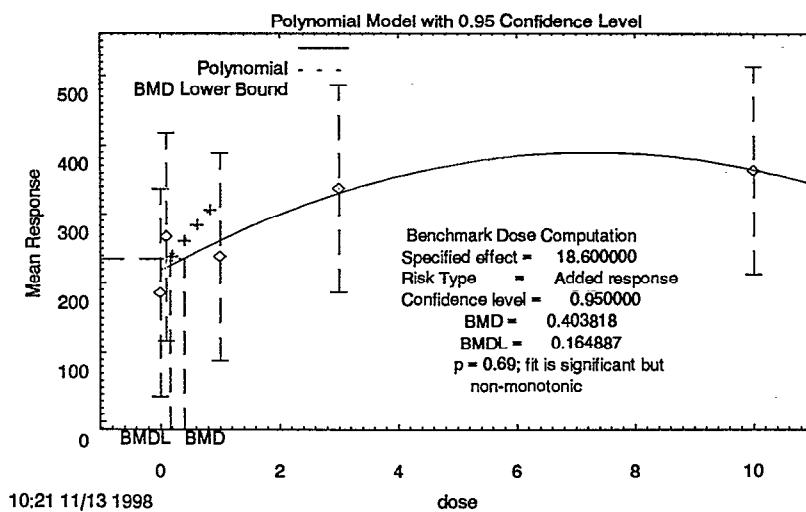
Developmental Neurotoxicity, PND 14 Motor Activity, Movement Data



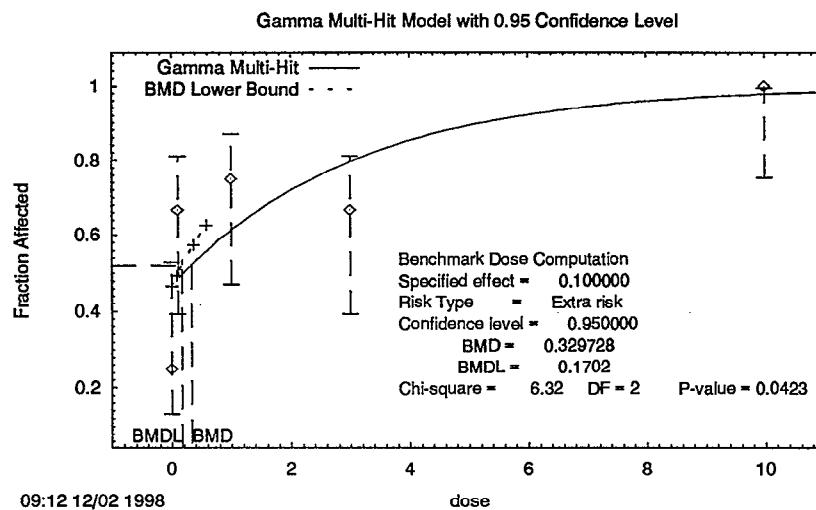
Developmental Neurotoxicity, PND 14 Motor Activity, Time Data



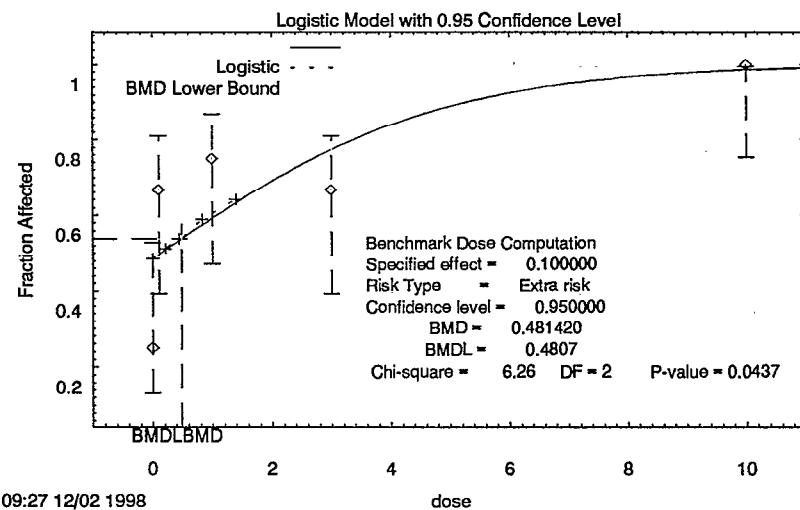
Developmental Neurotoxicity, PND 14 Motor Activity, Time Data



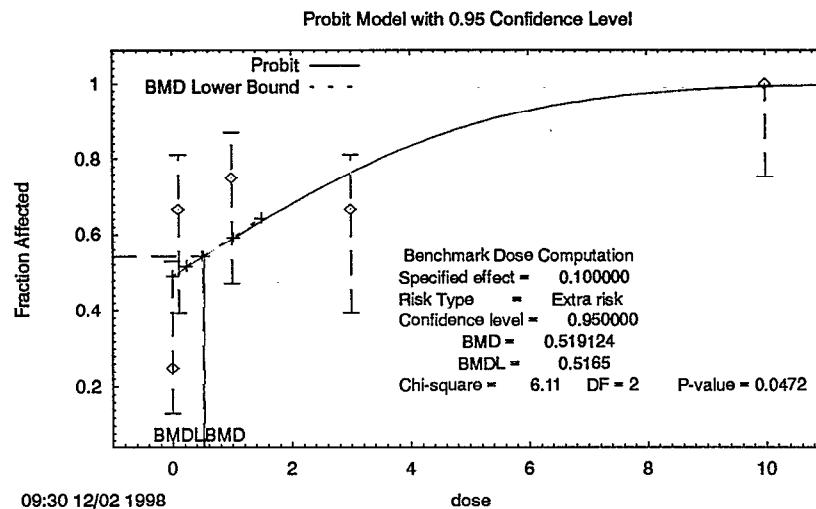
BMD Model of Incidence of Standard Histopathology from Developmental Neurotoxicity Study, PND5 Pups



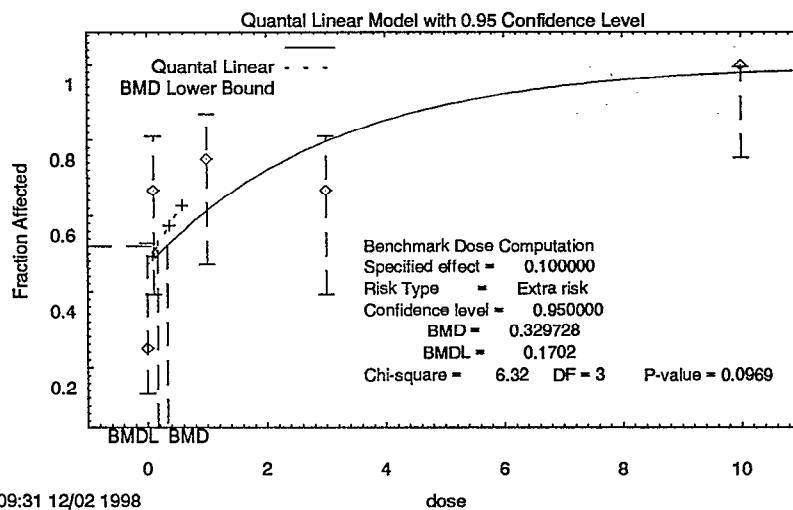
BMD Model of Incidence of Standard Histopathology from Developmental Neurotoxicity Study, PND5 Pups



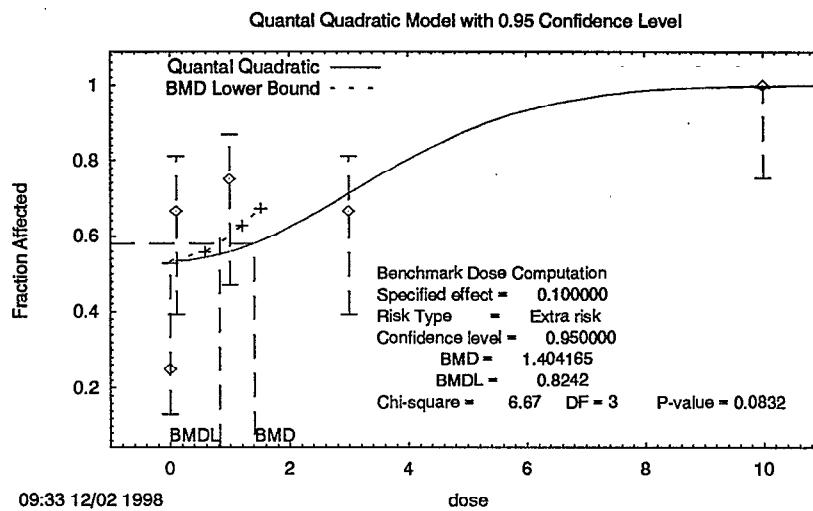
BMD Model of Incidence of Standard Histopathology from Developmental Neurotoxicity Study, PND5 Pups



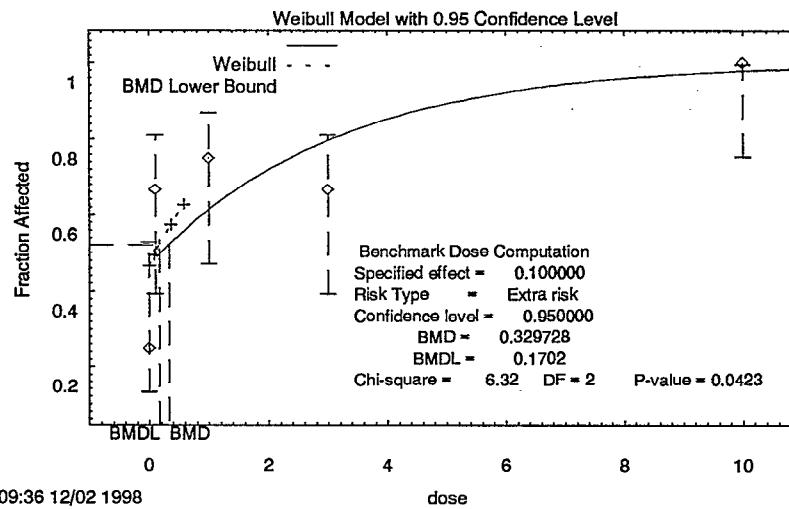
BMD Model of Incidence of Standard Histopathology from Developmental Neurotoxicity Study, PND5 Pups



BMD Model of Incidence of Standard Histopathology from Developmental Neurotoxicity Study, PND5 Pups



BMD Model of Incidence of Standard Histopathology from Developmental Neurotoxicity Study, PND5 Pups



Appendix A5 – Rabbit Developmental Toxicity (Seg II)**Table A5-1 – USEPA BMDs from fits to Rabbit Teratology (Seg II) Study, GD29 Females..A5-2****Table A5-2 – BMDLs from Rabbit Developmental Toxicology Study, GD29 time point.
BMRs at CTL - 10%, 20%, 40% of CTL.....A5-2**

Rabbit BMDs	A5-3
Power Model ln(T4)	A5-3
Linear Model to ln(T4)	A5-4
Polynomial Model to ln(T4)	A5-5
Power Model to arithmetic T4*	A5-6

Figures follow for the above fits except for *.

Table A5-1 – USEPA BMDs from fits to Rabbit Teratology (Seg II) Study, GD29 Females

Endpoint	p of fit	BMD	BMDL	NOAEL/ LOAEL	BMD: N(L)OAEL	BMDL: N(L)OAEL	BMR
TSH, ln TSH						NA	no effect of dose
T3, ln T3						NA	no effect of dose
T4	0.06	0.54	Lower limit includes 0	0.1	5.4	NA	0.187
ln (T4)	0.0503	1.69	0.002	0.1	16.9	0.02	0.1053

* LOAEL; otherwise, value is NOAEL

Table A5-2 – BMDLs from Rabbit Developmental Toxicology Study, GD29 time point.
BMRs at CTL - 10%, 20%, 40% of CTL. Underlined values from non-monotonic quadratic fits.

	p of fit	-10%	-20%	-40%	mean	NOAEL	
T4	0.06	Lower limit includes 0	Lower limit includes 0	0.63*	1.874	0.1	
ln(T4)	0.05	0.0018	0.033	7.278		0.1	
T3						no effect	
ln(T3)						no effect	
TSH						no effect	
ln(TSH)						no effect	

*BMDL calculation failed at a number of values. This means BMDL value may not be accurate.

Rabbit BMDs

Power Model ln(T4) – Female rabbits. GD29
 Input Data File: RABT4.SET
 Thu Oct 15 07:51:26 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[\text{dose}] = \text{control} + \text{slope} * \text{dose}^{\text{power}}$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

The sign of the slope is not restricted

Total number of dose groups = 6

Total number of records with missing values = 0

Default Initial Parameter Values

var_const = 0.242601

control = 0.684

slope = -0.346828

power = 0.0988158

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.245328	0.0283311
control	0.544653	0.0591854
slope	-0.0852209	0.0187154
power	0.401821	0.137875

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	control	slope	power
var_const	1	0.0011	-0.0035	-0.015
control	0.0011	1	-0.72	-0.075
slope	-0.0035	-0.72	1	0.24
power	-0.015	-0.075	0.24	1

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu_i + e_{ij}$
 $\text{Var}\{e_{ij}\} = \sigma^2$

Model A2: $Y_{ij} = \mu_i + e_{ij}$

$\text{Var}\{e_{ij}\} = \sigma^2$

Model R: $Y_i = \mu_i + e_i$

$\text{Var}\{e_i\} = \sigma^2$

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	34.286937	7	27.286937
A2	44.411451	12	32.411451
fitted	30.386894	4	26.386894
R	-281.187164	2	-283.187164

Test 1: Does response and/or variances differ among Dose levels

(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test -2*log(Likelihood Ratio) p-value

Test 1	630.948	<.00001
Test 2	20.249	0.001122
Test 3	7.80008	0.05033

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

The p-value for Test 2 is less than .05. Variances may not be homogeneous

Benchmark Dose Computation

Specified effect = 0.105300

Risk Type = Added response

Confidence level = 0.950000

BMD = 1.693030

BMDL = 0.001822

Linear Model to ln(T4) rabbit
 Input Data File: RABT4.SET
 Thu Oct 15 07:59:40 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[\text{dose}] = \beta_0 + \beta_1 \cdot \text{dose} + \beta_2 \cdot \text{dose}^2 + \dots$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

Signs of the polynomial coefficients are not restricted

Total number of dose groups = 6

Total number of records with missing values = 0

Default Initial Parameter Values

var_const = 0.242601

$\beta_0 = 0.461367$

$\beta_1 = -0.00503722$

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.248865	0.0287364
β_0	0.461367	0.0487407
β_1	-0.00503722	0.00113829

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	β_0	β_1
var_const	1	5.7e-010	8.1e-011
β_0	5.7e-010	1	-0.55
β_1	8.1e-011	-0.55	1

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu(i) + e(ij)$
 $\text{Var}\{e(ij)\} = \sigma^2$

Model A2: $Y_{ij} = \mu(i) + e(ij)$
 $\text{Var}\{e(ij)\} = \sigma^2(i)$

Model R: $Y_i = \mu + e(i)$
 $\text{Var}\{e(i)\} = \sigma^2$

Model	Log(likelihood)	DF
A1	34.286937	7
A2	44.411451	12
fitted	29.313502	3
R	-281.187164	2

Test 1: Does response and/or variances differ among dose levels

(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	p-value
Test 1	630.948	<0.00001
Test 2	20.249	0.001122
Test 3	9.94687	0.04133

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

The p-value for Test 2 is less than .05. Variances may not be homogeneous

The p-value for Test 3 is less than .05. You may want to try a different model

Benchmark Dose Computation

Specified effect = 0.105300 90% OF CONTROL

Risk Type = Added response

Confidence level = 0.950000

BMD = 20.904404

BMDL = 15.225306

Likelihoods of Interest

Polynomial Model to ln(T4) Rabbit
Input Data File: RABT4.SET

Thu Oct 15 08:10:39 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[\text{dose}] = \beta_0 + \beta_1 \cdot \text{dose} + \beta_2 \cdot \text{dose}^2 + \dots$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

Signs of the polynomial coefficients are not restricted

Total number of dose groups = 6

Total number of records with missing values = 0

Default Initial Parameter Values

var_const = 0.242601

beta_0 = 0.487155

beta_1 = -0.00999095

beta_2 = 4.94721e-005

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.247388	0.0285659
beta_0	0.487155	0.0557187
beta_1	-0.00999095	0.0053577
beta_2	4.94721e-005	5.22923e-005

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	beta_0	beta_1	beta_2
var_const	1	2.3e-009	4.3e-010	9.6e-011
beta_0	2.3e-009	1	-0.58	0.49
beta_1	4.3e-010	-0.58	1	-0.98
beta_2	9.6e-011	0.49	-0.98	1

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu(i) + e(ij)$
 $\text{Var}\{e(ij)\} = \sigma^2$

Model A2: $Y_{ij} = \mu(i) + e(ij)$
 $\text{Var}\{e(ij)\} = \sigma^2(i)$

Model R: $Y_i = \mu + e(i)$
 $\text{Var}\{e(i)\} = \sigma^2$

Likelihoods of Interest

Model	Log(likelihood)	DF
A1	34.286937	7
A2	44.411451	12
fitted	29.759696	4
R	-281.187164	2

Test 1: Does response and/or variances differ among dose levels

(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test -2*log(Likelihood Ratio) p-value

Test 1	630.948	<.00001
Test 2	20.249	0.001122
Test 3	9.05448	0.02858

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

The p-value for Test 2 is less than .05. Variances may not be homogeneous

The p-value for Test 3 is less than .05. You may want to try a different model

Benchmark Dose Computation

Specified effect = 0.105300

Risk Type = Added response

Confidence level = 0.950000

BMD = 11.155783

BMDL = 5.827807

Test 3 p = 0.02858 not sig fit

Power Model to arithmetic T4 data; sig fit.
BMDL limit includes 0

Input Data File: RABT4.SET

Thu Oct 15 08:15:21 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[\text{dose}] = \text{control} + \text{slope} * \text{dose}^{\text{power}}$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

The sign of the slope is not restricted

Total number of dose groups = 6

Total number of records with missing values = 0

Default Initial Parameter Values

var_const = 0.463651

control = 2.081

slope = -0.544653

power = 0.0801675

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.46732	0.0539699
control	1.93705	0.0927956
slope	-0.221166	0.0483526
power	0.270102	0.10232

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	control	slope	power
var_const	1	0.0017	-0.004	-0.018
control	0.0017	1	-0.79	-0.096
slope	-0.004	-0.79	1	0.23
power	-0.018	-0.096	0.23	1

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu_{(i)} + e_{(ij)}$

$$\text{Var}\{e_{(ij)}\} = \sigma^2$$

Model A2: $Y_{ij} = \mu_{(i)} + e_{(ij)}$

$$\text{Var}\{e_{(ij)}\} = \sigma^2_{(i)}$$

Model R: $Y_i = \mu_i + e_i$

$$\text{Var}\{e_i\} = \sigma^2$$

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-14.291586	7	-21.291586
A2	-9.872695	12	-21.872695
fitted	-17.944498	4	-21.944498
R	-329.526117	2	-331.526117

Test 1: Does response and/or variances differ among Dose levels
(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	p-value
Test 1	630.469	<.00001
Test 2	8.83778	0.1157
Test 3	7.30582	0.06276

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

Benchmark Dose Computation

Specified effect = 0.187000

Risk Type = Added response

Confidence level = 0.950000

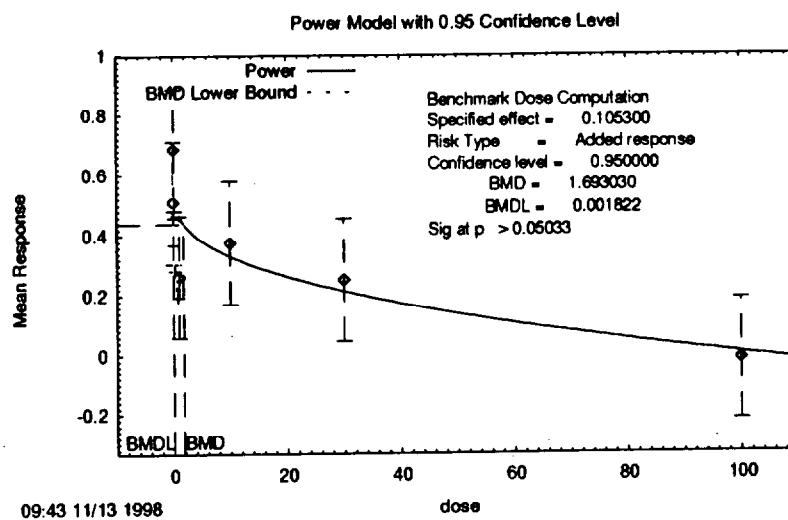
BMD = 0.537262

BMDL computation failed. Lower limit includes zero.

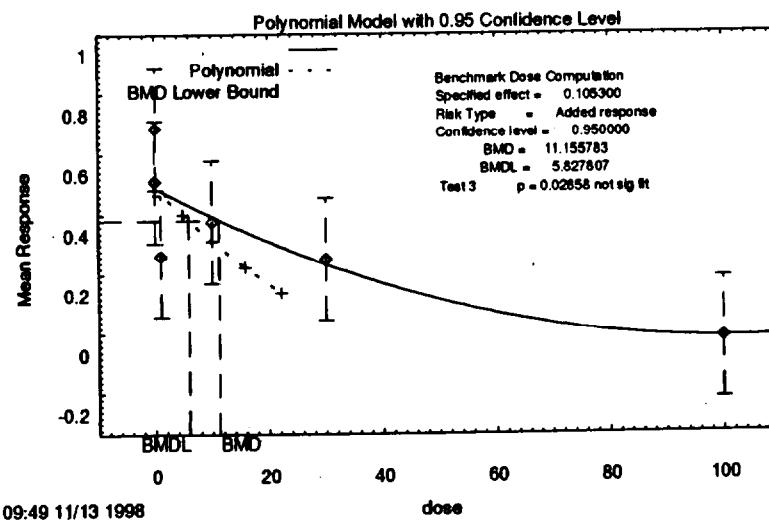
Test 3 p = 0.06276 significant

Fits to quadratic (non-monotonic) and linear funcs not significant.

Female Rabbit, GD29, LN(T4)

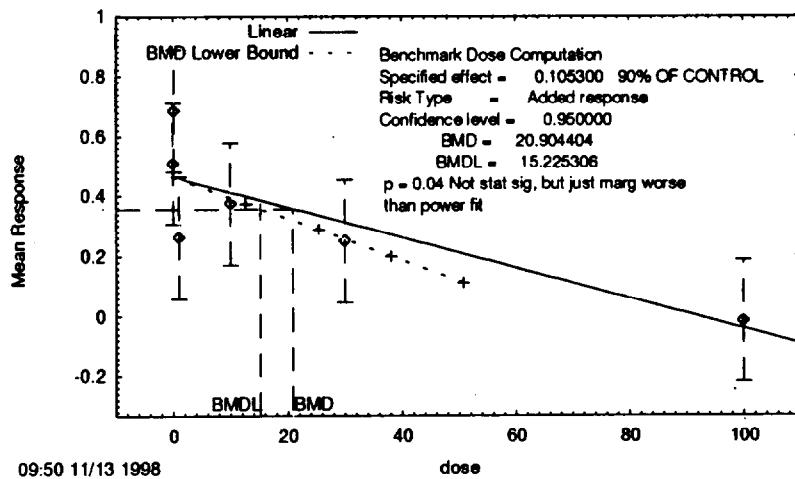


Female Rabbit, GD29, LN(T4)



Female Rabbit, GD29, LN(T4)

Linear Model with 0.95 Confidence Level



Appendix 6 – BMDs from Mouse Immunotoxicity Study

Table A6-1 – USEPA BMDs from fits to Mouse Immunotoxicology Study A6-2

Table A6-2 – BMDLs from Mouse Immunotoxicology Study.
BMRs at CTL - 10%, 20%, 40% of CTL..... A6-3

Mouse Immunotoxicity BMDs	A6-3
Power Model 14 day T4*	A6-3
Polynomial Model T4 14 day*	A6-4
Linear Model T4 14 days*	A6-5
Polynomial Model 90 day t4	A6-6
Linear Model 90 day t4	A6-7
Power Model 90 day T4	A6-8

*Figures follow for these fits.

Table A6-1 – USEPA BMDs from fits to Mouse Immunotoxicology Study

Endpoint	p of fit**	BMD	BMDL	NOAEL/ LOAEL	BMD: N(L)OAEL	BMDL: N(L)OAEL	BMR
14 day							
T4	linear	0.71	20.83	15.05	3.00	6.94	5.02
	quadratic	0.50	18.98	3.99	3.00	6.33	1.33
	power	0.50	21.02	2.89	3.00	7.01	0.96
90 day							
T4	0.84	.004	lower limit includes 0	0.10	.04	NA	0.36 0.64

** p > 0.05 denotes significant fit.

Table A6-2 – BMDLs from Mouse Immunotoxicology Study.

BMRs at CTL - 10%, 20%, 40% of CTL. Underlined values from non-monotonic quadratic fits.

	p of fit	-10%	-20%	-40%	mean	NOAEL	
T4 - 14 day	0.71	15.05	NC	NC	NC	3.00	Linear fit
T4 - 90 day	0.84	Lower limit includes 0	0.0009*	18.22*	3.60	0.10	Power fcn fit
T3						no effect	
ln(T3)						no effect	
TSH						no effect	
ln(TSH)						no effect	

*BMDL calculation failed at a number of values. This means BMDL value may not be accurate.

Mouse Immunotoxicity BMDs

Model Descriptions for likelihoods calculated

Power Model 14 day T4
Input Data File: MOUSE90.SET

Mon Nov 16 15:58:00 1998

BMDS MODEL RUN

The form of the response function is:

$Y[\text{dose}] = \text{control} + \text{slope} * \text{dose}^{\text{power}}$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

The sign of the slope is not restricted

Total number of dose groups = 5

Total number of records with missing values = 0

HERE is the pooled variance 0.286736

Default Initial Parameter Values
var_const = 0.296623
control = 3.463
slope = -0.194714
power = 0.235616

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.28939	0.0334163
control	3.38629	0.0508583
slope	-0.0151365	0.0035664
power	1.02081	0.32992

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	control	slope	power
var_const	1	-0.00025	0.00098	0.0055
control	-0.00025	1	-0.5	-0.046
slope	0.00098	-0.5	1	0.18
power	0.0055	-0.046	0.18	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	30	3.390	0.545	3.386	0.289
0.1000	30	3.328	0.605	3.385	0.289
1.0000	30	3.463	0.588	3.371	0.289
3.0000	30	3.300	0.529	3.340	0.289
30.0000	30	2.900	0.441	2.899	0.289

Model A1: $Y_{ij} = \mu_{(i)} + e_{(ij)}$
 $\text{Var}(e_{(ij)}) = \sigma^2$

Model A2: $Y_{ij} = \mu_{(i)} + e_{(ij)}$
 $\text{Var}(e_{(ij)}) = \sigma_{(i)}^2$

Model R: $Y_i = \mu + e_{(i)}$
 $\text{Var}(e_{(i)}) = \sigma^2$

Likelihoods of Interest

Model	Loglikelihood	DF	AIC
A1	18.689564	6	12.689564
A2	20.422673	10	10.422673
fitted	17.998624	4	13.998624
R	8.612997	2	6.612997

Test 1: Does response and/or variances differ among Dose levels
(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test -2*log(Likelihood Ratio) p-value

Test 1	20.1531	0.0004658
Test 2	3.46622	0.483
Test 3	1.38188	0.5011

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

Benchmark Dose Computation

Specified effect = 0.339000

Risk Type = Added response

Confidence level = 0.950000

BMD = 21.020832

BMDL = 2.892828

p = 0.50; fit is significant

Polynomial Model T4 14 day
Input Data File: MOUSE90.SET
Mon Nov 16 16:02:41 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[\text{dose}] = \beta_0 + \beta_1 \cdot \text{dose} + \beta_2 \cdot \text{dose}^2 + \dots$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

Signs of the polynomial coefficients are not restricted

Total number of dose groups = 5

Total number of records with missing values = 0

Default Initial Parameter Values

var_const	=	0.296623
beta_0	=	3.3909
beta_1	=	-0.02043
beta_2	=	0.000135322

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.289374	0.033414
beta_0	3.3909	0.0650325
beta_1	-0.02043	0.0452016
beta_2	0.000135322	0.00146553

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	beta_0	beta_1	beta_2
var_const	1	-1.3e-009	-5.5e-013	-1.1e-014
beta_0	-1.3e-009	1	-0.65	0.62
beta_1	-5.5e-013	-0.65	1	-1
beta_2	-1.1e-014	0.62	-1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	30	3.390	0.545	3.391	0.289
0.1000	30	3.328	0.605	3.389	0.289
1.0000	30	3.46	0.588	3.371	0.289
3.0000	30	3.301	0.529	3.331	0.289
30.0000	30	2.900	0.441	2.904	0.289

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu(i) + e(ij)$
 $\text{Var}(e(ij)) = \sigma^2$

Model A2: $Y_{ij} = \mu(i) + e(ij)$
 $\text{Var}(e(ij)) = \sigma^2(i)$

Model R: $Y_i = \mu + e(i)$
 $\text{Var}(e(i)) = \sigma^2$

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	18.689564	6	12.689564
A2	20.422673	10	10.422673
fitted	18.002621	4	14.002621
R	-289.827410	2	-291.827410

Test 1: Does response and/or variances differ among dose levels
(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test -2*log(Likelihood Ratio) p-value

Test 1	617.034	<.00001
Test 2	3.46622	0.483
Test 3	1.37389	0.5031

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

Benchmark Dose Computation

Specified effect = 0.339000
Risk Type = Added response
Confidence level = 0.950000
BMD = 18.979166
BMDL = 3.988034
p = 0.50: fit is significant

Linear Model T4 14 days
Input Data File: MOUSE90.SET
Mon Nov 16 16:06:58 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[\text{dose}] = \beta_0 + \beta_1 \cdot \text{dose} + \beta_2 \cdot \text{dose}^2 + \dots$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

Signs of the polynomial coefficients are not restricted

Total number of dose groups = 5

Total number of records with missing values = 0

Default Initial Parameter Values

var_const = 0.296623

$\beta_0 = 3.38717$

$\beta_1 = -0.0162708$

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.289391	0.0334159
β_0	3.38717	0.0509075
β_1	-0.0162708	0.00377349

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	β_0	β_1
var_const	1	2.9e-009	7.3e-012
β_0	2.9e-009	1	-0.51
β_1	7.3e-012	-0.51	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	30	3.390	0.545	3.387	0.289
0.1000	30	3.328	0.605	3.386	0.289
1.0000	30	3.463	0.588	3.371	0.289
3.0000	30	3.300	0.529	3.338	0.289
30.0000	30	2.900	0.441	2.899	0.289

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu_{ij} + e_{ij}$
 $\text{Var}(e_{ij}) = \sigma^2$

Model A2: $Y_{ij} = \mu_{ij} + e_{ij}$
 $\text{Var}(e_{ij}) = \sigma_{ij}^2$

Model R: $Y_i = \mu_i + e_i$
 $\text{Var}(e_i) = \sigma^2$

Likelihoods of Interest

Model	Log(Likelihood)	DF	AIC
A1	18.689564	6	12.689564
A2	20.422673	10	10.422673
fitted	17.998358	3	14.998358
R	-289.827410	2	-291.827410

Test 1: Does response and/or variances differ among dose levels
(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	p-value
Test 1	617.034	<.00001
Test 2	3.46622	0.483
Test 3	1.38241	0.7097

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

Benchmark Dose Computation

Specified effect = 0.339000

Risk Type = Added response

Confidence level = 0.950000

BMD = 20.834872

BMDL = 15.053805

p = .71: fit is significant

Polynomial Model 90 day t4
Input Data File: MOUSE90.SET

Mon Nov 16 15:43:37 1998

BMDS MODEL RUN

The form of the response function is:

$Y[dose] = \beta_0 + \beta_1 * dose + \beta_2 * dose^2 + \dots$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

Signs of the polynomial coefficients are not restricted

Total number of dose groups = 5

Total number of records with missing values = 0

Default Initial Parameter Values

var_const =	0.257008
beta_0 =	3.25279
beta_1 =	-0.189207
beta_2 =	0.00539337

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.278999	0.0518088
beta_0	3.26214	0.102166
beta_1	-0.188981	0.070178
beta_2	0.00537538	0.00227548

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	beta_0	beta_1	beta_2
var_const	1	-2.5e-008	1.5e-007	-1.6e-007
beta_0	-2.5e-008	1	-0.64	0.61
beta_1	1.5e-007	-0.64	1	-1
beta_2	-1.6e-007	0.61	-1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	12	3.600	0.640	3.262	0.279
0.1000	12	3.020	0.493	3.244	0.279
1.0000	10	2.850	0.474	3.084	0.279
3.0000	12	2.820	0.371	2.760	0.279
30.0000	12	2.430	0.514	2.592	0.279

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu(i) + e(ij)$
 $\text{Var}(e(ij)) = \sigma^2$

Model A2: $Y_{ij} = \mu(i) + e(ij)$
 $\text{Var}(e(ij)) = \sigma(i)^2$

Model R: $Y_i = \mu + e(i)$
 $\text{Var}(e(i)) = \sigma^2$

Likelihoods of Interest

Model	Log(Likelihood)	DF	AIC
A1	13.015163	6	7.015163
A2	14.807976	10	4.807976
fitted	8.019894	4	4.019894
R	-88.624846	2	-90.624846

Test 1: Does response and/or variances differ among dose levels
(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	p-value
Test 1	203.28	<.00001
Test 2	3.58563	0.465
Test 3	9.99054	0.00677

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels.

The p-value for Test 3 is less than .05. You may want to try a different model

Benchmark Dose Computation

Specified effect = 0.360000

Risk Type = Added response

Confidence level = 0.950000

BMD = 2.021150

BMDL = 1.221947

Linear Model 90 day t4
Input Data File: MOUSE90.SET

Mon Nov 16 15:45:05 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[\text{dose}] = \beta_0 + \beta_1 * \text{dose} + \beta_2 * \text{dose}^2 + \dots$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

Signs of the polynomial coefficients are not restricted

Total number of dose groups = 5

Total number of records with missing values = 0

Default Initial Parameter Values

var_const = 0.257008

beta_0 = 3.10385

beta_1 = -0.0234386

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.305843	0.0567936
beta_0	3.11421	0.0845202
beta_1	-0.0237828	0.00616028

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	beta_0	beta_1
var_const	1	-9.5e-010	-5.4e-008
beta_0	-9.5e-010	1	-0.51
beta_1	-5.4e-008	-0.51	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	12	3.600	0.640	3.114	0.306
0.1000	12	3.020	0.493	3.112	0.306
1.0000	10	2.850	0.474	3.090	0.306
3.0000	12	2.820	0.371	3.043	0.306
30.0000	12	2.430	0.514	2.401	0.306

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu_{(i)} + e_{(ij)}$
 $\text{Var}(e_{(ij)}) = \sigma^2$

Model A2: $Y_{ij} = \mu_{(i)} + e_{(ij)}$
 $\text{Var}(e_{(ij)}) = \sigma_{(i)}^2$

Model R: $Y_i = \mu_i + e(i)$
 $\text{Var}(e(i)) = \sigma^2$

Likelihoods of Interest

Model	Log(Likelihood)	DF	AIC
A1	13.015163	6	7.015163
A2	14.807976	10	4.807976
fitted	5.355852	3	2.355852
R	-88.624846	2	-90.624846

Test 1: Does response and/or variances differ among dose levels
(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test -2*log(Likelihood Ratio) p-value

Test	-2*log(Likelihood Ratio)	p-value
Test 1	203.28	<.00001
Test 2	3.58563	0.465
Test 3	15.3186	0.001564

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

The p-value for Test 3 is less than .05. You may want to try a different model

Benchmark Dose Computation

Specified effect = 0.360000

Risk Type = Added response

Confidence level = 0.950000

BMD = 15.136982

BMDL = 10.571053

Power Model 90 day T4
Input Data File: MOUSE90.SET
Mon Nov 16 15:46:01 1998

BMDS MODEL RUN

The form of the response function is:

$$Y[\text{dose}] = \text{control} + \text{slope} * \text{dose}^{\text{power}}$$

Dependent variable = MEAN

Independent variable = dose

var_power is set to 0

The sign of the slope is not restricted

Total number of dose groups = 5

Total number of records with missing values = 0

HERE is the pooled variance 0.234852

Default Initial Parameter Values
var_const = 0.257008
control = 3.6
slope = -0.743169
power = 0.119905

Parameter Estimates

Variable	Estimate	Std. Err.
var_const	0.236237	0.0438692
control	3.59596	0.126362
slope	-0.731857	0.124246
power	0.130005	0.129501

Asymptotic Correlation Matrix of Parameter Estimates

	var_const	control	slope	power
var_const	1	-0.001	0.0015	0.0069
control	-0.001	1	-0.86	-0.14
slope	0.0015	-0.86	1	0.22
power	0.0069	-0.14	0.22	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0.0000	12	3.600	0.640	3.596	0.236
0.1000	12	3.020	0.493	3.053	0.236
1.0000	10	2.850	0.474	2.864	0.236
3.0000	12	2.820	0.371	2.752	0.236
30.0000	12	2.430	0.514	2.457	0.236

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu_{(i)} + e_{(ij)}$
 $\text{Var}\{e_{(ij)}\} = \sigma^2$

Model A2: $Y_{ij} = \mu_{(i)} + e_{(ij)}$

$$\text{Var}\{e_{(ij)}\} = \sigma^2$$

Model R: $Y_{ij} = \mu_{(i)} + e_{(ij)}$
 $\text{Var}\{e_{(ij)}\} = \sigma^2$

Likelihoods of Interest

Model	Log(Likelihood)	DF	AIC
A1	13.015163	6	7.015163
A2	14.807976	10	4.807976
fitted	12.844624	4	8.844624
R	-5.455937	2	-7.455937

Test 1: Does response and/or variances differ among Dose levels
(A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test = -2 * log(Likelihood Ratio) p-value

Test 1	36.9422	<.00001
Test 2	3.58563	0.465
Test 3	0.341078	0.8432

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

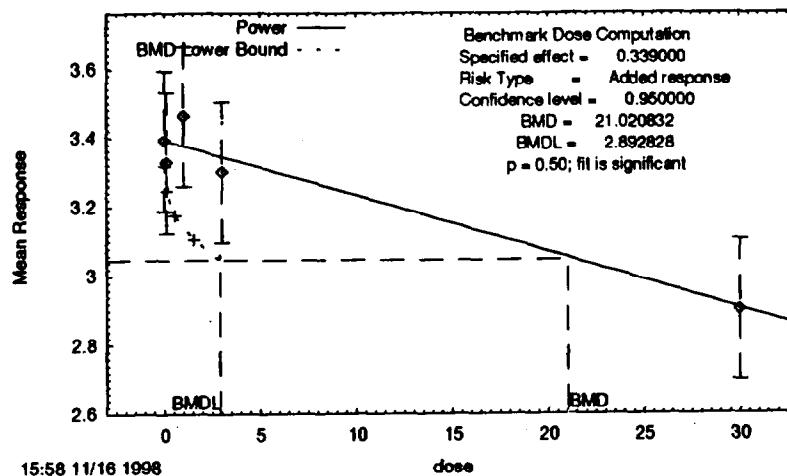
Benchmark Dose Computation

Specified effect = 0.360000
Risk Type = Added response
Confidence level = 0.950000
BMD = 0.004265

BMDL computation failed. Lower limit includes zero.

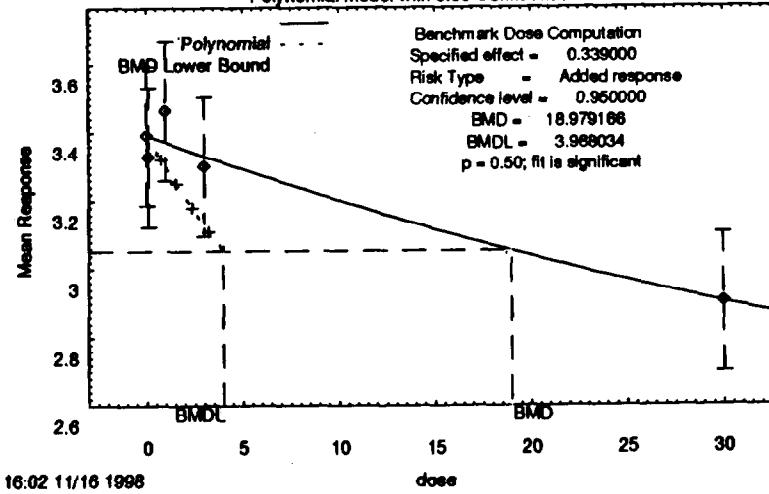
Mouse Immunotoxicity Study T4, 14 Days Exposure

Power Model with 0.95 Confidence Level



Mouse Immunotoxicity Study T4, 14 Days Exposure

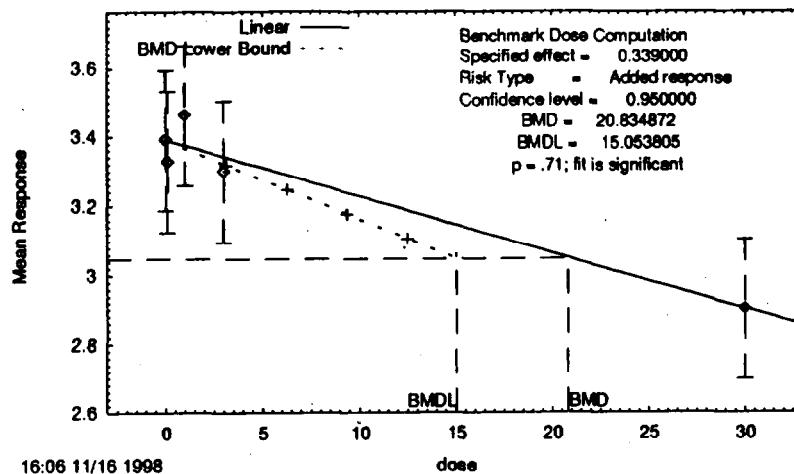
Polynomial Model with 0.95 Confidence Level



Mouse Immunotoxicity Study

T4, 14 Days Exposure

Linear Model with 0.95 Confidence Level



Appendix 7 – BMDs for Standard Histopathology Data

Table 7-1 – Caldwell 14 day study, Incidence of Follicular Hypertrophy/ Hyperplasia.....	A7-2
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BMDs for Standard Histopathology	A7-4
Caldwell 14 Day Study	A7-4
Gamma Model	A7-4
Probit Model	A7-5
Logistic Model	A7-6
Weibull Model	A7-7
Quantal Quadratic Model	A7-8
Quantal Linear Model	A7-9
Subchronic Study, 14 Day Timepoint	A7-10
Gamma Model	A7-10
Probit Model	A7-11
Logistic Model	A7-12
Weibull Model	A7-13
Quantal Quadratic Model	A7-14
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Multistage Model	A7-16
Subchronic Study, 90 Day Timepoint	A7-17
Gamma Model	A7-17
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Logistic Model	A7-19
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Developmental Neurotoxicity, PND5	A7-24
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Probit Model	A7-25
Logistic Model	A7-26
Weibull Model	A7-27
Quantal Quadratic Model	A7-28
Quantal Linear Model	A7-29
Figure A7-1 BMD Model fits for Standard Histopathology	A7-30

Table 7-1 – BMDs from Caldwell 14 day study, Incidence of Follicular Hypertrophy/Hyperplasia. BMDs reflect 10% extra risk.

Function	p of fit, df	BMD	BMDL	LOAEL	BMD: LOAEL	BMDL: LOAEL
Gamma	0.75,6	0.077	0.044	0.1	0.77	0.44
Logistic	0.70,6	0.123	0.115	0.1	1.23	1.15
Probit	0.71,6	0.135	0.0134	0.1	1.35	0.134
Quantal Linear	0.75,6	0.077	0.044	0.1	0.77	0.44
Quantal Quadratic	0.54,6	0.37	0.243	0.1	3.70	2.43
Weibull	0.746,6	0.077	0.044	0.1	0.77	0.44

Table 7-2 – BMDs from Subchronic Study, 14 Day Timepoint, Incidence of Follicular Hypertrophy/Hyperplasia Data. BMDs reflect 10% extra risk.

Function	p of fit, df	BMD	BMDL	NOAEL	BMD: NOAEL	BMDL: NOAEL
Gamma	0.39,3	5.32	2.10	1.0	5.32	2.10
Logistic	0.43,4	3.37	2.21	1.0	3.37	2.21
Probit	0.40,4	2.85	1.96	1.0	2.85	1.96
Quantal Linear	0.10,4	0.683	0.44	1.0	0.683	0.44
Quantal Quadratic	0.49,4	2.25	1.76	1.0	2.25	1.76
Weibull	0.39,3	5.45	3.37	1.0	5.45	3.37
Multistage	0.33, 3	2.25	1.25	1.0	2.25	1.25

Table 7-3 – BMDs from Subchronic Study, 90 Day Timepoint, Incidence of Follicular Hypertrophy/Hyperplasia Data. BMDs reflect 10% extra risk.

Function	p of fit, df	BMD	BMDL	NOAEL	BMD: NOAEL	BMDL: NOAEL
Gamma	0.14, 3	1.91	0.81	1.0	1.91	0.81
Logistic	0.21, 4	2.50	2.18	1.0	2.50	2.18
Probit	0.18, 4	2.20	1.93	1.0	2.20	1.93
Quantal Linear	0.02, 4	0.55	0.36	1.0	0.55	0.36
Quantal Quadratic	0.22, 4	1.93	1.46	1.0	1.93	1.46
Weibull	0.14, 3	2.23	0.82	1.0	2.23	0.82
Multistage	0.13, 3	1.93	0.87	1.0	1.93	0.87

Table 7-4 – BMDs from Developmental Neurotoxicity Study, PND5, Incidence of Follicular Hyperplasia/Hypertrophy Data. BMDs reflect 10% extra risk.

Function	p of fit, df	BMD	BMDL	LOAEL	BMD: LOAEL	BMDL: LOAEL
Gamma	0.85, 3	0.234	0.10	0.1	2.34	1.0
Logistic	0.84, 3	0.35	0.27	0.1	3.5	2.7
Probit	0.84, 3	0.379	0.376	0.1	3.79	3.76
Quantal Linear	0.85, 3	0.234	0.10	0.1	2.34	1.0
Quantal Quadratic	0.74, 3	0.96	0.53	0.1	9.6	5.3
Weibull	0.85, 3	0.234	0.10	0.1	2.34	1.0

BMDs for Standard Histopathology**Caldwell 14 Day Study**

Gamma Model, Version Number: 1.1.0b
 Input Data File: C:\BMDSCALDSHFREQ.D

Tue Dec 22 09:26:47 1998

BMDS MODEL RUN

The form of the probability function is:

P[response] =
 background + (1-background) * CumGamma(slope * dose, power).
 where CumGamma(.) is the cumulative Gamma distribution function

Dependent variable = FH

Independent variable = dose

Power parameter is restricted as power >= 1

Total number of observations = 8

Total number of records with missing values = 0

Maximum number of iterations = 250

Relative Function Convergence = 2.22045e-016

Parameter Convergence = 1.49012e-008

Default Initial Parameter Values
 Background = 0.333333
 Slope = 0.318067
 Power = 1.2

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0.411763	0.120519
Slope	1.37712	1.63298
Power	1	1.15747

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Slope	Power
Background	1	0.403	0.5464
Slope	0.403	1	0.9549
Power	0.5464	0.9549	1

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	DF	P-value
Full model	-27.372			
Fitted model	-29.1452	3.54636	6	0.616385
Reduced model	-46.1186	33.9468		
	24.2516e-008			

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size
0.0000	0.4118	4.941	4	12
0.1100	0.4945	5.439	6	11
0.4500	0.6835	8.202	10	12
1.1100	0.8724	10.469	9	12
2.6300	0.9843	11.811	12	12
4.6200	0.9990	11.988	12	12
11.4500	1.0000	12.000	12	12
22.5100	1.0000	12.000	12	12
Chi-square = 3.49 DF = 6 P-value = 0.7459				

Benchmark Dose Computation

Benchmark response = 0.100000

Risk Type = Extra risk

Confidence level = 0.950000

BMD = 0.076508

BMDL = 0.0437

Analysis of Deviance Table

Probit Model, Version Number: 1.1.0b
 Input Data File: C:\BMDS\CALDSHFREQ.D(D)
 Tue Dec 22 09:30:18 1998

Model	Log(likelihood)	Deviance	DF	P-value
Full model	-27.372			
Fitted model	-29.357	3.96989	6	0.680752
Reduced model	-46.1186	33.5232		
	17.0417e-009			

Goodness of Fit

BMDS MODEL RUN

The form of the probability function is:

$P[\text{response}] = \text{CumNorm}(\text{Intercept} + \text{Slope} * \text{Dose})$.

where CumNorm(.) is the cumulative normal distribution function

Dependent variable = FH

Independent variable = dose

Slope parameter is not restricted

Total number of observations = 8

Total number of records with missing values = 0

Maximum number of iterations = 250

Relative Function Convergence has been set to:

2.22045e-016

Parameter Convergence has been set to: 1.49012e-008

Dose	Est._Prob.	Expected	Observed	Size
0.0000	0.4656	5.587	4	12
0.1100	0.5090	5.599	6	11
0.4500	0.6404	7.685	10	12
1.1100	0.8446	10.135	9	12
2.6300	0.9941	11.930	12	12
4.6200	1.0000	12.000	12	12
11.4500	1.0000	12.000	12	12
22.5100	1.0000	12.000	12	12

Chi-square = 3.73 DF = 6 P-value = 0.7130

Benchmark Dose Computation

Benchmark response = 0.100000

Risk Type = Extra risk

Confidence level = 0.950000

BMD = 0.135300

BMDL = 0.1338

Default Initial Parameter Values

Intercept = 0.914409

Slope = 0.101925

Parameter Estimates

Variable	Estimate	Std. Err.
Intercept	-0.0863689	0.333092
Slope	0.991005	0.423756

Asymptotic Correlation Matrix of Parameter Estimates

	Intercept	Slope
Intercept	1	-0.6818
Slope	-0.6818	1

Full model	-27.372
Fitted model	-29.3926
Reduced model	-46.1186
	17.3043e-009

Logistic Model, Version Number: 1.1.0b
Input Data File: C:\BMDS\CALDSHFREQ.(D)

Tue Dec 22 09:31:39 1998

BMDS MODEL RUN

The form of the probability function is:

$$P[\text{response}] = 1/[1+\text{EXP}(-\text{intercept}-\text{slope}*\text{dose})]$$

Dependent variable = FH

Independent variable = dose

Slope parameter is not restricted

Total number of observations = 8

Total number of records with missing values = 0

Maximum number of iterations = 250

Relative Function Convergence has been set to:

2.22045e-016

Parameter Convergence has been set to: 1.49012e-008

Default Initial Parameter Values

intercept = 1.57985

slope = 0.185143

Parameter Estimates

Variable	Estimate	Std. Err.
intercept	-0.169585	0.482491
slope	1.75984	0.494968

Asymptotic Correlation Matrix of Parameter Estimates

	intercept	slope
intercept	1	-0.5073
slope	-0.5073	1

Analysis of Deviance Table

Model Log(likelihood) Deviance DF P-value

Goodness of Fit					
Dose	Est._Prob.	Expected	Observed	Size	
0.0000	0.4577	5.492	4	12	
0.1100	0.5060	5.566	6	11	
0.4500	0.6508	7.809	10	12	
1.1100	0.8562	10.274	9	12	
2.6300	0.9886	11.863	12	12	
4.6200	0.9997	11.996	12	12	
11.4500	1.0000	12.000	12	12	
22.5100	1.0000	12.000	12	12	

Chi-square = 3.82 DF = 6 P-value = 0.7013

Benchmark Dose Computation

Benchmark response = 0.100000

Risk Type = Extra risk

Confidence level = 0.950000

BMD = 0.123496

BMDL = 0.1150

Analysis of Deviance Table

Weibull Model, Version Number: 1.1.0b
 Input Data File: C:\BMDS\CALDSHFREQ.(D)

Tue Dec 22 09:41:31 1998

BMDS MODEL RUN

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{slope} * \text{dose}^{\text{power}})]$$

Dependent variable = FH

Independent variable = dose

Power parameter is restricted as power >= 1

Total number of observations = 8

Total number of records with missing values = 0

Maximum number of iterations = 250

Relative Function Convergence has been set to:
 2.22045e-016

Parameter Convergence has been set to: 1.49012e-008

Default Initial Parameter Values
 Background = 0.333333
 Slope = 0.318067
 Power = 1.2

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0.411763	0.369966
Slope	1.37712	1.30305
Power	1	1.3315

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Slope	Power
Background	1	-0.9093	0.8926
Slope	-0.9093	1	-0.8942
Power	0.8926	-0.8942	1

Model	Log(likelihood)	Deviance	DF	P-value
Full model	-27.372			
Fitted model	-29.1452	3.54636	6	0.616385
Reduced model	-46.1186	33.9468		
	24.2516e-008			

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size
0.0000	0.4118	4.941	4	12
0.1100	0.4945	5.439	6	11
0.4500	0.6835	8.202	10	12
1.1100	0.8724	10.469	9	12
2.6300	0.9843	11.811	12	12
4.6200	0.9990	11.988	12	12
11.4500	1.0000	12.000	12	12
22.5100	1.0000	12.000	12	12

Chi-square = 3.49 DF = 6 P-value = 0.7459

Benchmark Dose Computation

Benchmark response = 0.100000

Risk Type = Extra risk

Confidence level = 0.950000

BMD = 0.076508

BMDL = 0.0437

Quantal Quadratic Model, Version Number:
1.1.0b
Input Data File: CNBMDS\CALDSHFREQ.(D)

Tue Dec 22 09:44:27 1998

BMDS MODEL RUN

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{slope} * \text{dose}^2)]$$

Dependent variable = FH

Independent variable = dose

Total number of observations = 8

Total number of records with missing values = 0

Maximum number of iterations = 250

Relative Function Convergence has been set to:

2.22045e-016

Parameter Convergence has been set to: 1.49012e-008

Default Initial Parameter Values

Background = 0.333333

Slope = 0.0341458

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0.522658	0.126493
Slope	0.771618	0.517817

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Slope
Background	1	-0.4536
Slope	-0.4536	1

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	DF	P-value
-------	-----------------	----------	----	---------

Full model	-27.372
Fitted model	-30.0706
Reduced model	-46.1186
	5.39715
	32.096
	0.493974
	11.4674e-008

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size
0.0000	0.5227	6.272	4	12
0.1100	0.5271	5.798	6	11
0.4500	0.5917	7.101	10	12
1.1100	0.8155	9.786	9	12
2.6300	0.9977	11.972	12	12
4.6200	1.0000	12.000	12	12
11.4500	1.0000	12.000	12	12
22.5100	1.0000	12.000	12	12

Chi-square = 5.01 DF = 6 P-value = 0.5427

Benchmark Dose Computation

Benchmark response = 0.100000

Risk Type = Extra risk

Confidence level = 0.950000

BMD = 0.369520

BMDL = 0.2426

Quantal Linear Model, Version Number:	1.1.0b
Input Data File: C:\NBMDSCALDSHFREQ.(D)	

Tue Dec 22 09:45:27 1998

BMDS MODEL RUN

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{slope} * \text{dose})]$$

Dependent variable = FH
 Independent variable = dose

Total number of observations = 8
 Total number of records with missing values = 0
 Maximum number of iterations = 250
 Relative Function Convergence has been set to:
 2.22045e-016
 Parameter Convergence has been set to: 1.49012e-008

Default Initial Parameter Values
 Background = 0.333333
 Slope = 0.531545

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0.411763	0.166809
Slope	1.37712	0.583237

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Slope
Background	1	-0.5508
Slope	-0.5508	1

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	DF	P-value
-------	-----------------	----------	----	---------

Full model	-27.372
Fitted model	-29.1452
Reduced model	-46.1186

3.54636	6	0.737792
33.9468	1	5.664e-009

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size
0.0000	0.4118	4.941	4	12
0.1100	0.4945	5.439	6	11
0.4500	0.6835	8.202	10	12
1.1100	0.8724	10.469	9	12
2.6300	0.9843	11.811	12	12
4.6200	0.9990	11.988	12	12
11.4500	1.0000	12.000	12	12
22.5100	1.0000	12.000	12	12

Chi-square = 3.49 DF = 6 P-value = 0.7459

Benchmark Dose Computation

Benchmark response = 0.100000

Risk Type = Extra risk

Confidence level = 0.950000

BMD = 0.076508

BMDL = 0.0437

Subchronic Study, 14 Day Timepoint
 Gamma Model, Version Number: 1.1.0b
 Input Data File: C:\BMDSSUBCHFREQ.D

Tue Dec 22 10:01:21 1998

BMDS MODEL RUN

The form of the probability function is:

P[response] =
 background + (1-background)*CumGamma[slope*dose,pow
 er].
 where CumGamma(.) is the cumulative Gamma
 distribution function

Dependent variable = FH14

Independent variable = dose

Power parameter is restricted as power>-1

Total number of observations = 6

Total number of records with missing values = 0

Maximum number of iterations = 250

Relative Function Convergence = 2.22045e-016

Parameter Convergence = 1.49012e-008

Default Initial Parameter Values

Background = 0.01
 Slope = 0.137745
 Power = 1.2

Slope	0.4519	1	1
Power	0.4519	1	1

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	DF	P-value
Full model	-13.9442			
Fitted model	-15.7779	3.66738	3	0.299693
Reduced model	-47.9161	64.2763		
	23.1781e-012			

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size
0.0000	0.0233	0.419	1	18
0.0100	0.0233	0.349	0	15
0.0500	0.0233	0.395	1	17
0.2000	0.0233	0.372	0	16
1.0000	0.0233	0.465	0	20
10.0000	0.8889	16.000	16	18

Chi-square = 2.99 DF = 3 P-value = 0.3935

Benchmark Dose Computation

Benchmark response = 0.100000

Risk Type = Extra risk

Confidence level = 0.950000

BMD = 5.317014

BMDL = 2.1023

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0.0232558	0.0180152
Slope	2.09056	3.37528e+006
Power	15.9764	2.92887e+007

Asymptotic Correlation Matrix of Parameter Estimates

Background	Slope	Power
Background	1	0.4519

Probit Model, Version Number: 1.1.0b
 Input Data File: CNBMDS\SUBCHFREQ.(D)
 Tue Dec 22 09:56:44 1998

Model	Log(likelihood)	Deviance	DF	P-value
Full model	-13.9442			
Fitted model	-16.2197	4.55087	4	0.336559
Reduced model	-47.9161	63.3928		
	14.9329e-012			

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size
0.0000	0.0191	0.344	1	18
0.0100	0.0192	0.288	0	15
0.0500	0.0197	0.336	1	17
0.2000	0.0218	0.349	0	16
1.0000	0.0375	0.750	0	20
10.0000	0.8841	15.914	16	18
Chi-square = 4.05 DF = 4 P-value = 0.3987				

BMDS MODEL RUN

The form of the probability function is:

$$P[\text{response}] = \text{CumNorm}(\text{Intercept} + \text{Slope} * \text{Dose}),$$

where CumNorm(.) is the cumulative normal distribution function

Dependent variable = FH14

Independent variable = dose

Slope parameter is not restricted

Total number of observations = 6

Total number of records with missing values = 0

Maximum number of iterations = 250

Relative Function Convergence has been set to:

2.22045e-016

Parameter Convergence has been set to: 1.49012e-008

Benchmark Dose Computation

Benchmark response = 0.100000

Risk Type = Extra risk

Confidence level = 0.950000

BMD = 2.853663

BMDL = 1.9644

Default Initial Parameter Values

Intercept = -2.34096

Slope = 0.347496

Parameter Estimates

Variable	Estimate	Std. Err.
Intercept	-2.16617	1.89722
Slope	0.33597	0.193104

Asymptotic Correlation Matrix of Parameter Estimates

	Intercept	Slope
Intercept	1	-0.9769
Slope	-0.9769	1

Analysis of Deviance Table

Logistic Model, Version Number: 1.1.0b
 Input Data File: C:\BMDS\SUBCHFREQ.(D)

Tue Dec 22 09:58:25 1998

BMDS MODEL RUN

The form of the probability function is:

$$P[\text{response}] = 1/[1+\text{EXP}(-\text{intercept}-\text{slope}*\text{dose})]$$

Dependent variable = FH14

Independent variable = dose

Slope parameter is not restricted

Total number of observations = 6

Total number of records with missing values = 0

Maximum number of iterations = 250

Relative Function Convergence has been set to:

2.22045e-016

Parameter Convergence has been set to: 1.49012e-008

Full model	-13.9442			
Fitted model	-16.0913	4.29414	4	0.367659
Reduced model	-47.9161	63.6495		
14.5568e-012				

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size
0.0000	0.0198	0.356	1	18
0.0100	0.0199	0.298	0	15
0.0500	0.0203	0.345	1	17
0.2000	0.0218	0.349	0	16
1.0000	0.0329	0.657	0	20
10.0000	0.8855	15.939	16	18

Chi-square = 3.80 DF = 4 P-value = 0.4334

Benchmark Dose Computation

Benchmark response = 0.100000

Risk Type = Extra risk

Confidence level = 0.950000

BMD = 3.372552

BMDL = 2.2093

Default Initial Parameter Values

intercept = -4.00277
 slope = 0.59546

Parameter Estimates

Variable	Estimate	Std. Err.
intercept	-4.12857	2.45301
slope	0.616944	0.248958

Asymptotic Correlation Matrix of Parameter Estimates

	intercept	slope
intercept	1	-0.9509
slope	-0.9509	1

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	DF	P-value
-------	-----------------	----------	----	---------

Background	1	2.003e-009	-0.005878
Slope	2.003e-009	-1	1.001
Power	-0.005878	1.001	-1

Weibull Model. Version Number: 1.1.0b
Input Data File: C:\BMDS\SUBCHFREQ.(D)

Tue Dec 22 09:59:54 1998

BMDS MODEL RUN

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{slope} * \text{dose}^{\text{power}})]$$

Dependent variable = FH14

Independent variable = dose

Power parameter is restricted as power>=1

Total number of observations = 6

Total number of records with missing values = 0

Maximum number of iterations = 250

Relative Function Convergence has been set to:

2.22045e-016

Parameter Convergence has been set to: 1.49012e-008

Default Initial Parameter Values

Background = 0.01

Slope = 0.137745

Power = 1.2

Warning: Maximum iteration may be not large enough.

Iterations reaches the maximum.

Warning: Maximum iteration may be not large enough.

Iterations reaches the maximum.

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0.0232561	0.106566
Slope	2.22702e-005	0.000189748
Power	4.99011	3.69754

Asymptotic Correlation Matrix of Parameter Estimates

Background	Slope	Power
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Analysis of Deviance Table

Model	Log(likelihood)	Deviance	DF	P-value
Full model	-13.9442			
Fitted model	-15.7784	3.66829	3	0.299582
Reduced model	-47.9161	64.2754		
		23.1792e-012		

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size
0.0000	0.0233	0.419	1	18
0.0100	0.0233	0.349	0	15
0.0500	0.0233	0.395	1	17
0.2000	0.0233	0.372	0	16
1.0000	0.0233	0.466	0	20
10.0000	0.8892	16.006	16	18

Chi-square = 2.99 DF = 3 P-value = 0.3934

Benchmark Dose Computation

Benchmark response = 0.100000

Risk Type = Extra risk

Confidence level = 0.950000

BMD = 5.450645

BMDL = 3.3718

Quantal Quadratic Model, Version Number:
1.1.0b
Input Data File: C:\BMDSSUBCHFREQ.(D)

Tue Dec 22 10:00:09 1998

BMDS MODEL RUN

The form of the probability function is:

P[response] = background +
(1-background)*[1-EXP(-slope*dose^2)]

Dependent variable = FH14
Independent variable = dose

Total number of observations = 6
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to:
2.22045e-016
Parameter Convergence has been set to: 1.49012e-008

Default Initial Parameter Values
Background = 0.01
Slope = 0.0232096

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0.0232861	0.106548
Slope	0.020871	0.00682106

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Slope
Background	1	-0.16
Slope	-0.16	1

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	DF	P-value
Full model	-13.9442			
Fitted model	-16.2161	4.54379	4	0.337387
Reduced model	-47.9161	63.3999		
	14.9221e-012			

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size
0.0000	0.0233	0.419	1	18
0.0100	0.0233	0.349	0	15
0.0500	0.0233	0.397	1	17
0.2000	0.0241	0.386	0	16
1.0000	0.0435	0.869	0	20
10.0000	0.8788	15.819	16	18

Chi-square = 3.44 DF = 4 P-value = 0.4868

Benchmark Dose Computation

Benchmark response = 0.100000

Risk Type = Extra risk

Confidence level = 0.950000

BMD = 2.246815

BMDL = 1.7613

Default Initial Parameter Values
Background = 0.01
Slope = 0.0232096

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0.0232861	0.106548
Slope	0.020871	0.00682106

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Slope
Background	1	-0.16
Slope	-0.16	1

Analysis of Deviance Table

Quantal Linear Model. Version Number:
1.1.0b
Input Data File: C:\BMDSSUBCHFREQ.(D)

Tue Dec 22 10:00:22 1998

BMDS MODEL RUN

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{slope} * \text{dose})]$$

Dependent variable = FH14
Independent variable = dose

Total number of observations = 6
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to:
2.22045e-016
Parameter Convergence has been set to: 1.49012e-008

Default Initial Parameter Values
Background = 0.01
Slope = 0.208273

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0.0206967	0.107597
Slope	0.154166	0.049871

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Slope
Background	1	-0.2292
Slope	-0.2292	1

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	DF	P-value
Full model	-13.9442			
Fitted model	-19.814	11.7396	4	0.0193968
Reduced model	-47.9161	56.2041		
	14.7151e-011			

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size
0.0000	0.0207	0.373	1	18
0.0100	0.0222	0.333	0	15
0.0500	0.0282	0.480	1	17
0.2000	0.0504	0.807	0	16
1.0000	0.1606	3.212	0	20
10.0000	0.7904	14.227	16	18

Chi-square = 7.73 DF = 4 P-value = 0.1019

Benchmark Dose Computation

Benchmark response = 0.100000

Risk Type = Extra risk

Confidence level = 0.950000

BMD = 0.683422

BMDL = 0.4401

Multistage Model. Version Number: 1.1.0b
 Input Data File: C:\BMDSSUBCHFREQ.(D)

Tue Dec 22 10:00:36 1998

BMDS MODEL RUN

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{beta1} * \text{dose}^1 - \text{beta2} * \text{dose}^2)]$$

The parameter betas are restricted to be positive

Dependent variable = FH14

Independent variable = dose

Total number of observations = 6

Total number of records with missing values = 0

Total number of parameters in model = 3

Total number of specified parameters = 0

Degree of polynomial = 2

Maximum number of iterations = 250

Relative Function Convergence has been set to:

2.22045e-016

Parameter Convergence has been set to: 1.49012e-008

Default Initial Parameter Values

Background = 0.0189176

Beta(1) = 0

Beta(2) = 0.0217771

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0.0232861	0.150383
Beta(1)	6.56267e-021	4.3854
Beta(2)	0.020871	0.437507

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)	Beta(2)
Background	1	-0.7057	0.7038
Beta(1)	-0.7057	1	-0.9999
Beta(2)	0.7038	-0.9999	1

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	DF	P-value
Full model	-13.9442			
Fitted model	-16.2161	4.54379	3	0.208418
Reduced model	-47.9161	63.3999	2	4.309e-012

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size
0.0000	0.0233	0.419	1	18
0.0100	0.0233	0.349	0	15
0.0500	0.0233	0.397	1	17
0.2000	0.0241	0.386	0	16
1.0000	0.0435	0.869	0	20
10.0000	0.8788	15.819	16	18

Chi-square = 3.44 DF = 3 P-value = 0.3284

Benchmark Dose Computation

Benchmark response = 0.100000

Risk Type = Extra risk

Confidence level = 0.950000

BMD = 2.246815

BMDL = 1.2549

Subchronic Study, 90 Day Timepoint

Gamma Model, Version Number: 1.1.0b
 Input Data File: C:\BMDS\SUBCHIFREQ.(D)

Tue Dec 22 10:14:07 1998

BMDS MODEL RUN

The form of the probability function is:

$P[\text{response}] = \text{background} + (1-\text{background}) * \text{CumGamma}[\text{slope} * \text{dose}, \text{power}]$,
 where CumGamma(.) is the cumulative Gamma distribution function

Dependent variable = FH90

Independent variable = dose

Power parameter is restricted as power>=1

Total number of observations = 6

Total number of records with missing values = 0

Maximum number of iterations = 250

Relative Function Convergence = 2.22045e-016

Parameter Convergence = 1.49012e-008

Default Initial Parameter Values.

Background = 0.01

Slope = 0.181471

Power = 1.2

Background	1	0.34	0.3949
Slope	0.34	1	0.9442
Power	0.3949	0.9442	1

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	DF	P-value
Full model	-14.1113			
Fitted model	-16.7976	5.37257	3	0.146462
Reduced model	-50.9134	68.2315		
	28.1357e-013			

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size
0.0000	0.0304	0.548	2	18
0.0100	0.0304	0.457	0	15
0.0500	0.0304	0.518	0	17
0.2000	0.0306	0.490	0	16
1.0000	0.0492	0.985	1	20
10.0000	0.9445	17.002	17	18

Chi-square = 5.48 DF = 3 P-value = 0.1400

Benchmark Dose Computation

Benchmark response = 0.100000

Risk Type = Extra risk

Confidence level = 0.950000

BMD = 1.909209

BMDL = 0.8136

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0.030447	0.0209563
Slope	0.639102	0.397584
Power	3.1907	2.39255

Asymptotic Correlation Matrix of Parameter Estimates

Background Slope Power

Probit Model, Version Number: 1.1.0b
 Input Data File: C:\BMDSS\SUBCHFREQ.D

Tue Dec 22 10:14:46 1998

BMDS MODEL RUN

The form of the probability function is:

P[response] = CumNorm(Intercept+Slope*Dose).

where CumNorm(.) is the cumulative normal distribution function

Dependent variable = FH90

Independent variable = dose

Slope parameter is not restricted

Total number of observations = 6

Total number of records with missing values = 0

Maximum number of iterations = 250

Relative Function Convergence has been set to:

2.22045e-016

Parameter Convergence has been set to: 1.49012e-008

Default Initial Parameter Values

Intercept = -2.27362

Slope = 0.388147

Parameter Estimates

Variable	Estimate	Std. Err.
Intercept	-1.92221	1.28838
Slope	0.350065	0.137458

Asymptotic Correlation Matrix of Parameter Estimates

	Intercept	Slope
Intercept	1	-0.9337
Slope	-0.9337	1

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	DF	P-value
Full model	-14.1113			
Fitted model	-16.9189	5.61514	4	0.229793
Reduced model	-50.9134	67.989	11.2077e-012	

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size
0.0000	0.0273	0.491	2	18
0.0100	0.0275	0.413	0	15
0.0500	0.0284	0.483	0	17
0.2000	0.0320	0.512	0	16
1.0000	0.0580	1.159	1	20
10.0000	0.9428	16.970	17	18

Chi-square = 6.24 DF = 4 P-value = 0.1820

Benchmark Dose Computation

Benchmark response = 0.100000

Risk Type = Extra risk

Confidence level = 0.950000

BMD = 2.198798

BMDL = 1.9290

Logistic Model, Version Number: 1.1.0b
 Input Data File: C:\BMDS\SUBCHFREQ.D

Tue Dec 22 10:15:25 1998

BMDS MODEL RUN

The form of the probability function is:

$$P[\text{response}] = 1/[1+\text{EXP}(-\text{intercept}-\text{slope}*\text{dose})]$$

Dependent variable = FH90

Independent variable = dose

Slope parameter is not restricted

Total number of observations = 6

Total number of records with missing values = 0

Maximum number of iterations = 250

Relative Function Convergence has been set to:

2.22045e-016

Parameter Convergence has been set to: 1.49012e-008

Default Initial Parameter Values

intercept = -3.93493

slope = 0.677934

Parameter Estimates

Variable	Estimate	Std. Err.
intercept	-3.52475	2.42027
slope	0.633854	0.256471

Asymptotic Correlation Matrix of Parameter Estimates

	intercept	slope
intercept	1	-0.9156
slope	-0.9156	1

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	DF	P-value
Full model	-14.1113			

Fitted model	-16.8798	5.5369	4	0.236505
Reduced model	-50.9134	68.0672		
	11.1795e-012			

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size
0.0000	0.0286	0.515	2	18
0.0100	0.0288	0.432	0	15
0.0500	0.0295	0.502	0	17
0.2000	0.0324	0.518	0	16
1.0000	0.0526	1.052	1	20
10.0000	0.9434	16.981	17	18

Chi-square = 5.91 DF = 4 P-value = 0.2062

Benchmark Dose Computation

Benchmark response = 0.100000

Risk Type = Extra risk

Confidence level = 0.950000

BMD = 2.501715

BMDL = 2.1840

Weibull Model, Version Number: 1.1.0b
Input Data File: C:\BMDS\SUBCHFREQ.D

Tue Dec 22 10:16:23 1998

BMDS MODEL RUN

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{slope} * \text{dose}^{\text{power}})]$$

Dependent variable = FH90

Independent variable = dose

Power parameter is restricted as power>=1

Total number of observations = 6

Total number of records with missing values = 0

Maximum number of iterations = 250

Relative Function Convergence has been set to:
2.22045e-016

Parameter Convergence has been set to: 1.49012e-008

Default Initial Parameter Values

Background = 0.01

Slope = 0.181471

Power = 1.2

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	DF	P-value
Full model	-14.1113			
Fitted model	-16.8046	5.38647	3	0.145589
Reduced model	-50.9134	68.2176		

28.1757e-013

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size
0.0000	0.0307	0.552	2	18
0.0100	0.0307	0.460	0	15
0.0500	0.0307	0.522	0	17
0.2000	0.0312	0.499	0	16
1.0000	0.0480	0.960	1	20
10.0000	0.9446	17.002	17	18

Chi-square = 5.44 DF = 3 P-value = 0.1421

Benchmark Dose Computation

Benchmark response = 0.100000

Risk Type = Extra risk

Confidence level = 0.950000

BMD = 2.231745

BMDL = 0.8185

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0.0306934	0.133678
Slope	0.017996	0.73706
Power	2.20139	17.7592

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Slope	Power
Background	-1	1.278	-1.279
Slope	1.278	-1	1
Power	-1.279	1	-1

Quantal Quadratic Model, Version Number:
 1.1.0b
 Input Data File: C:\BMDSSUBCHFREQ.(D)

Tue Dec 22 10:16:37 1998

BMDS MODEL RUN

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{slope} * \text{dose}^2)]$$

Dependent variable = FH90

Independent variable = dose

Total number of observations = 6

Total number of records with missing values = 0

Maximum number of iterations = 250

Relative Function Convergence has been set to:

2.22045e-016

Parameter Convergence has been set to: 1.49012e-008

	Full model	-14.1113	Fitted model	-16.8237	5.42477	4	0.246422
	Reduced model	-50.9134		68.1793	1	1.14e-012	

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size
0.0000	0.0293	0.528	2	18
0.0100	0.0293	0.440	0	15
0.0500	0.0294	0.499	0	17
0.2000	0.0304	0.486	0	16
1.0000	0.0564	1.128	1	20
10.0000	0.9429	16.972	17	18

Chi-square = 5.72 DF = 4 P-value = 0.2211

Benchmark Dose Computation

Benchmark response = 0.100000

Risk Type = Extra risk

Confidence level = 0.950000

BMD = 1.928448

BMDL = 1.4577

Default Initial Parameter Values

Background = 0.01

Slope = 0.0305772

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0.0293056	0.106764
Slope	0.028331	0.0099296

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Slope
Background	1	-0.1285
Slope	-0.1285	1

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	DF	P-value
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Quantal Linear Model, Version Number:
1.1.0b
Input Data File: CNBMDSSUBCHFREQ.(D)

Tue Dec 22 10:17:04 1998

BMDS MODEL RUN

The form of the probability function is:

$P[\text{response}] = \text{background} + (1-\text{background}) * [1-\text{EXP}(-\text{slope} * \text{dose})]$

Dependent variable = FH90
Independent variable = dose

Total number of observations = 6
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to:
2.22045e-016
Parameter Convergence has been set to: 1.49012e-008

Default Initial Parameter Values
Background = 0.01
Slope = 0.274387

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0.0253361	0.107668
Slope	0.189908	0.0595781

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Slope
Background	1	-0.209
Slope	-0.209	1

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	DF	P-value
-------	-----------------	----------	----	---------

Full model	-14.1113
Fitted model	-20.1333
Reduced model	-50.9134
	12.0438
	61.5603
	18.7108e-012

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size
0.0000	0.0253	0.456	2	18
0.0100	0.0272	0.408	0	15
0.0500	0.0345	0.587	0	17
0.2000	0.0617	0.987	0	16
1.0000	0.1939	3.878	1	20
10.0000	0.8541	15.374	17	18

Chi-square = 11.27 DF = 4 P-value = 0.0237

Benchmark Dose Computation

Benchmark response = 0.100000

Risk Type = Extra risk

Confidence level = 0.950000

BMD = 0.554799

BMDL = 0.3569

Multistage Model, Version Number: 1.1.0b
Input Data File: C:\BMDSSUBCHFREQ.D

Tue Dec 22 10:17:37 1998

BMDS MODEL RUN

The form of the probability function is:

$$P[\text{response}] = \text{background} + (\text{1-background}) * [1 - \text{EXP}(-\text{beta1} * \text{dose}^1 - \text{beta2} * \text{dose}^2)]$$

The parameter betas are restricted to be positive

Dependent variable = FH90

Independent variable = dose

Total number of observations = 6

Total number of records with missing values = 0

Total number of parameters in model = 3

Total number of specified parameters = 0

Degree of polynomial = 2

Maximum number of iterations = 250

Relative Function Convergence has been set to:

2.22045e-016

Parameter Convergence has been set to: 1.49012e-008

Default Initial Parameter Values

Background = 0.0274748

Beta(1) = 0

Beta(2) = 0.0286245

	Background	Beta(1)	Beta(2)
Background	1	-0.4449	0.3866
Beta(1)	-0.4449	1	-0.9499
Beta(2)	0.3866	-0.9499	1

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	DF	P-value
Full model	-14.1113			
Fitted model	-16.8237	5.42477	3	0.143208
Reduced model	-50.9134	68.1793		
	28.2823e-013			

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size
0.0000	0.0293	0.528	2	18
0.0100	0.0293	0.440	0	15
0.0500	0.0294	0.499	0	17
0.2000	0.0304	0.486	0	16
1.0000	0.0564	1.128	1	20
10.0000	0.9429	16.972	17	18

Chi-square = 5.72 DF = 3 P-value = 0.1261

Benchmark Dose Computation

Benchmark response = 0.100000

Risk Type = Extra risk

Confidence level = 0.950000

BMD = 1.928448

BMDL = 0.8700

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0.0293056	0.119214
Beta(1)	2.67024e-023	0.303628
Beta(2)	0.028331	0.0317638

Asymptotic Correlation Matrix of Parameter Estimates

Developmental Neurotoxicity, PND5

Gamma Model, Version Number: 1.1.0b
 Input Data File: CNBMDSD\DEVNTFREQ.D

Tue Dec 22 10:28:47 1998

BMDS MODEL RUN

The form of the probability function is:

P[response] =
 background + (1-background)*CumGamma[slope*dose,pow
 er].
 where CumGamma(.) is the cumulative Gamma
 distribution function

Dependent variable = fh

Independent variable = dose

Power parameter is restricted as power>=1

Total number of observations = 5

Total number of records with missing values = 0

Maximum number of iterations = 250

Relative Function Convergence = 2.22045e-016

Parameter Convergence = 1.49012e-008

Default Initial Parameter Values

Background = 0.333333

Slope = 0.414833

Power = 1.2

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0.445771	0.14909
Slope	0.450054	0.940071
Power	1	1.76025

**Asymptotic Correlation Matrix of Parameter
 Estimates**

	Background	Slope	Power
Background	1	0.4061	0.551
Slope	0.4061	1	0.9559
Power	0.551	0.9559	1

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	DF	P-value
Full model	-16.8301			
Fitted model	-17.2537	0.847244	3	0.654671
Reduced model	-22.1579	9.80847	2	0.0074151

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size
0.0000	0.4458	2.675	2	6
0.1000	0.4702	3.291	4	7
1.0000	0.6466	5.820	6	9
3.0000	0.8563	4.282	4	5
10.0000	0.9938	8.945	9	9

Chi-square = 0.80 DF = 3 P-value = 0.8505

Benchmark Dose Computation

Benchmark response = 0.100000

Risk Type = Extra risk

Confidence level = 0.950000

BMD = 0.234106

BMDL = 0.1011

**Asymptotic Correlation Matrix of Parameter
 Estimates**

Variable	Estimate	Std. Err.
Background	0.445771	0.14909
Slope	0.450054	0.940071
Power	1	1.76025

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	DF	P-value
Full model	-16.8301			
Fitted model	-17.2563	0.852504	3	0.836872
Reduced model	-22.1579	9.80321	1	0.0017421

Tue Dec 22 10:31:07 1998

BMDS MODEL RUN

The form of the probability function is:

$$P[\text{response}] = \text{CumNorm}(\text{Intercept} + \text{Slope} * \text{Dose}),$$

where CumNorm(.) is the cumulative normal distribution function

Dependent variable = fh

Independent variable = dose

Slope parameter is not restricted

Total number of observations = 5

Total number of records with missing values = 0

Maximum number of iterations = 250

Relative Function Convergence has been set to:

2.22045e-016

Parameter Convergence has been set to: 1.49012e-008

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size
0.0000	0.4765	2.859	2	6
0.1000	0.4902	3.432	4	7
1.0000	0.6130	5.517	6	9
3.0000	0.8363	4.181	4	5
10.0000	0.9997	8.997	9	9

Chi-square = 0.84 DF = 3 P-value = 0.8404

Benchmark Dose Computation

Benchmark response = 0.100000

Risk Type = Extra risk

Confidence level = 0.950000

BMD = 0.379478

BMDL = 0.3756

Default Initial Parameter Values

Intercept = 0.00352656

Slope = 0.259741

Parameter Estimates

Variable	Estimate	Std. Err.
Intercept	-0.0590537	0.431641
Slope	0.346082	0.266435

Asymptotic Correlation Matrix of Parameter Estimates

	Intercept	Slope
Intercept	1	-0.6517
Slope	-0.6517	1

Full model	-16.8301			
Fitted model	-17.269	0.877805	3	0.83078
Reduced model	-22.1579	9.77791	1	0.0017662

Logistic Model, Version Number: 1.1.0b
Input Data File: C:\BMDS\DEVNTFREQ.D

Tue Dec 22 10:31:53 1998

BMDS MODEL RUN

The form of the probability function is:

$$P[\text{response}] = 1/[1+\text{EXP}(-\text{intercept}-\text{slope}*\text{dose})]$$

Dependent variable = fh

Independent variable = dose

Slope parameter is not restricted

Total number of observations = 5

Total number of records with missing values = 0

Maximum number of iterations = 250

Relative Function Convergence has been set to:

2.22045e-016

Parameter Convergence has been set to: 1.49012e-008

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size
0.0000	0.4694	2.816	2	6
0.1000	0.4846	3.392	4	7
1.0000	0.6198	5.579	6	9
3.0000	0.8471	4.235	4	5
10.0000	0.9975	8.978	9	9

Chi-square = 0.85 DF = 3 P-value = 0.8378

Benchmark Dose Computation

Benchmark response = 0.100000

Risk Type = Extra risk

Confidence level = 0.950000

BMD = 0.347421

BMDL = 0.2713

Default Initial Parameter Values

intercept = -0.0770638

slope = 0.471944

Parameter Estimates

Variable	Estimate	Std. Err.
intercept	-0.122721	0.596716
slope	0.611565	0.260909

Asymptotic Correlation Matrix of Parameter Estimates

	intercept	slope
intercept	1	-0.4235
slope	-0.4235	1

Analysis of Deviance Table

Model Log(likelihood) Deviance DF P-value

Analysis of Deviance Table

Weibull Model, Version Number: 1.1.0b
 Input Data File: CNBMDS\DEVNTFREQ.D

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BMDS MODEL RUN

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{slope} * \text{dose}^{\text{power}})]$$

Dependent variable = fh

Independent variable = dose

Power parameter is restricted as power>=1

Total number of observations = 5

Total number of records with missing values = 0

Maximum number of iterations = 250

Relative Function Convergence has been set to:

2.22045e-016

Parameter Convergence has been set to: 1.49012e-008

Default Initial Parameter Values

Background = 0.333333

Slope = 0.414833

Power = 1.2

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0.445771	0.261729
Slope	0.450054	0.807509
Power	1	1.0773

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Slope	Power
Background	1	-0.7653	0.6806
Slope	-0.7653	1	-0.9299
Power	0.6806	-0.9299	1

Model	Log(likelihood)	Deviance	DF	P-value
Full model	-16.8301			
Fitted model	-17.2537	0.847244	3	0.654671
Reduced model	-22.1579	9.80847	2	0.0074151

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size
0.0000	0.4458	2.675	2	6
0.1000	0.4702	3.291	4	7
1.0000	0.6466	5.820	6	9
3.0000	0.8563	4.282	4	5
10.0000	0.9938	8.945	9	9

Chi-square = 0.80 DF = 3 P-value = 0.8505

Benchmark Dose Computation

Benchmark response = 0.100000

Risk Type = Extra risk

Confidence level = 0.950000

BMD = 0.234106

BMDL = 0.1011

Quantal Quadratic Model, Version Number:
1.1.0b
Input Data File: C:\BMD\\$DEVNTFREQ.(D)

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BMDS MODEL RUN

The form of the probability function is:

$$P[\text{response}] = \text{background} + \\ (1-\text{background}) * [1-\text{EXP}(-\text{slope} * \text{dose}^2)]$$

Dependent variable = fh

Independent variable = dose

Total number of observations = 5

Total number of records with missing values = 0

Maximum number of iterations = 250

Relative Function Convergence has been set to:

2.22045e-016

Parameter Convergence has been set to: 1.49012e-008

Default Initial Parameter Values

Background = 0.333333

Slope = 0.0778655

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0.515863	0.161744
Slope	0.115491	0.130501

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Slope
Background	1	-0.4283
Slope	-0.4283	1

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	DF	P-value
Full model	-16.8301			
Fitted model	-17.4738	1.28736	3	0.732137
Reduced model	-22.1579	9.36835	1	0.0022076

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size
0.0000	0.5159	3.095	2	6
0.1000	0.5164	3.615	4	7
1.0000	0.5687	5.118	6	9
3.0000	0.8288	4.144	4	5
10.0000	1.0000	9.000	9	9

Chi-square = 1.27 DF = 3 P-value = 0.7370

Benchmark Dose Computation

Benchmark response = 0.100000

Risk Type = Extra risk

Confidence level = 0.950000

BMD = 0.955136

BMDL = 0.5263

Quantal Linear Model, Version Number:
1.1.0b
Input Data File: C:\BMDS\DEVNTFREQ.D

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BMDS MODEL RUN

The form of the probability function is:

$$P[\text{response}] = \text{background} + \\ (1-\text{background}) * [1-\text{EXP}(-\text{slope} * \text{dose})]$$

Dependent variable = fh

Independent variable = dose

Total number of observations = 5

Total number of records with missing values = 0

Maximum number of iterations = 250

Relative Function Convergence has been set to:

2.22045e-016

Parameter Convergence has been set to: 1.49012e-008

Default Initial Parameter Values

Background = 0.333333

Slope = 0.607517

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0.445771	0.191749
Slope	0.450054	0.29707

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Slope
Background	1	-0.4912
Slope	-0.4912	1

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	DF	P-value
Full model	-16.8301			
Fitted model	-17.2537	0.847244	3	0.838137
Reduced model	-22.1579	9.80847	1	0.0017371

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size
0.0000	0.4458	2.675	2	6
0.1000	0.4702	3.291	4	7
1.0000	0.6466	5.820	6	9
3.0000	0.8563	4.282	4	5
10.0000	0.9938	8.945	9	9

Chi-square = 0.80 DF = 3 P-value = 0.8505

Benchmark Dose Computation

Benchmark response = 0.100000

Risk Type = Extra risk

Confidence level = 0.950000

BMD = 0.234106

BMDL = 0.1011

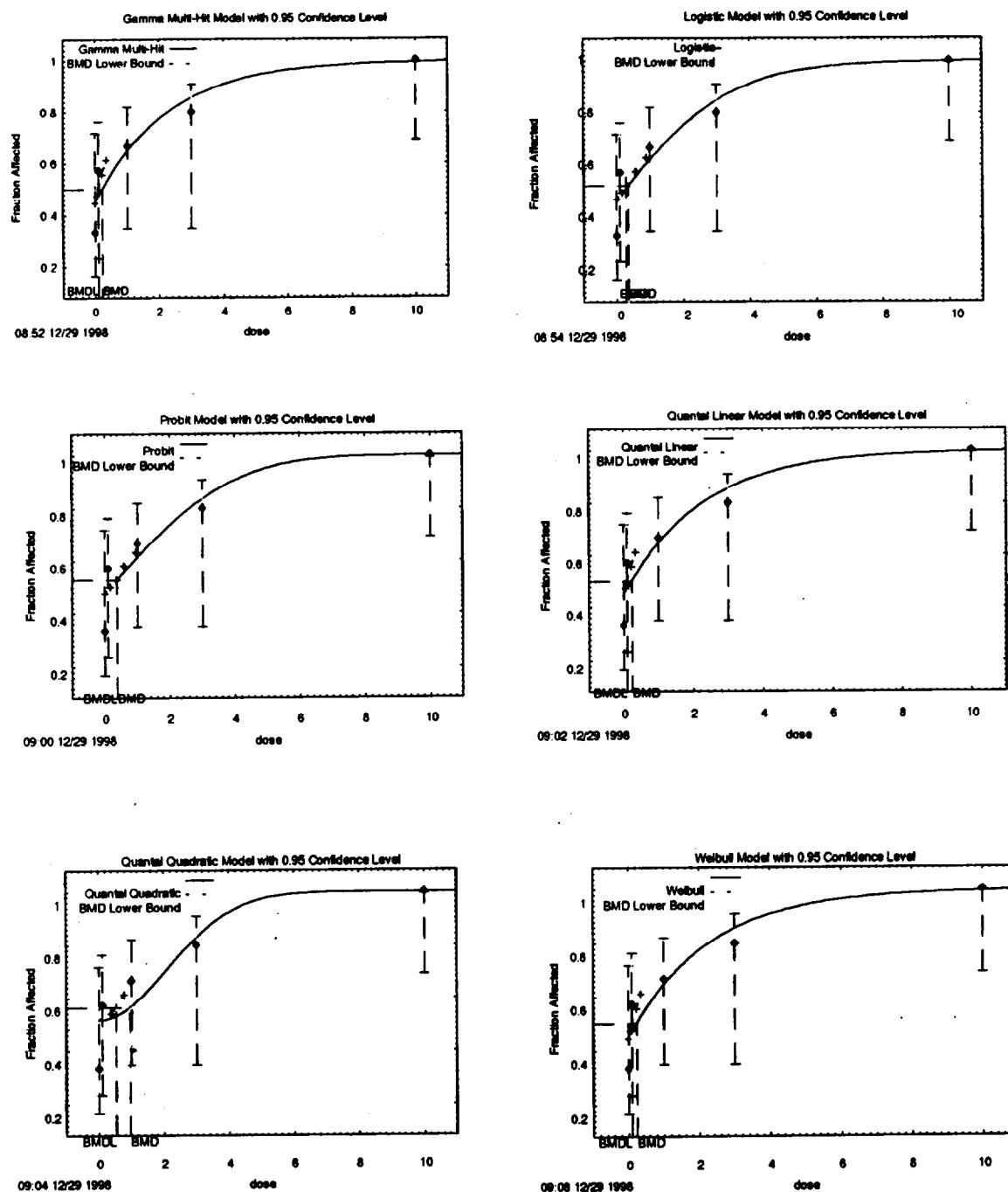


Figure A7-1. Benchmark dose model fits to dichotomized standard histopathology incidence data from Developmental Neurotoxicity study (Argus, 1998a, York, 1998c). Error bars show 95% confidence intervals around data points.